Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents

Volume 3 Final Report
Current Health Status of Test Subjects

Committee on Toxicology
Board on Toxicology and Environmental Health Hazards
Commission on Life Sciences
National Research Council

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This report is the third volume in a series prepared for a study that investigated possible delayed and long-term effects of experimental chemicals administered to soldiers at the U.S. Army Laboratories, Edgewood, Maryland. The Edgewood tests, conducted over a 20-year period ending in 1975, were intended to investigate the immediate and short-term human-performance effects of short-term exposure to various chemicals with warfare potential and the subjects' responses to therapy for such effects.

Volume 1 of the series (National Research Council, Committee on Toxicology. Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents. Vol. 1. Anticholinesterases and Anticholinergics. Washington, D.C.: National Academy Press, 1982) was concerned with the possible long-term effects of 15 anticholinesterases and 24 anticholinergic chemicals.
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Information in Volume 3 is based on the results of a questionnaire regarding current health status of test subjects. Edgewood test subjects who were alive and could be located received a mailed questionnaire; 82% of those who received the questionnaire responded to it. Subjects tested with anticholinesterase chemicals, anticholinergic chemicals, cholinesterase reactivators, or psychochemicals did not differ significantly from control subjects or from those tested with other classes of drugs in their replies to questions about their current health status. Almost 90% of all these respondents reported no health problems related to the exposures under scrutiny, and 79% reported good to excellent health. Subjects tested with irritants and vesicants, including those who developed skin burns from mustard gas, reported no increased prevalence of significant skin cancer or other adverse health effects. The experimental methods and the available comparison groups were such that only large effects were likely to be uncovered.

Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents

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Current Health Status of Test Subjects

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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PREFACE

In the spring of 1980, the Department of the Army asked the Committee on Toxicology of the National Research Council's Board on Toxicology and Environmental Health Hazards to study the possible chronic or delayed adverse health effects incurred by servicemen who had been exposed experimentally to various chemicals at the U.S. Army Laboratories, Aberdeen Proving Ground, Edgewood, Maryland, during 1955-1975. The Edgewood tests were conducted to learn how potential chemical warfare agents might affect humans over a short period and how such affected humans might respond to therapy for the effects of such agents. The Army believed that relevant information could not be obtained from animal experimentation alone and that it was necessary to confirm animal findings by using human volunteers.

Some 6,720 soldiers took part in this program. To understand the extent to which they might have experienced unanticipated long-term or delayed adverse effects, an extensive search for reports, records, and other data was undertaken. The search and the study and evaluation of all available information on the five major categories of chemicals involved (anticholinesterases, anticholinergics, cholinesterase reactivators, psychochemicals, and irritants and vesicants) were accomplished by panels of experts under the direction of the Committee on Toxicology.

The present report was prepared by a coordinating committee made up of the chairmen of the five panels involved in earlier reports, epidemiologists who had served on those panels, and one newly appointed person. It is based largely on the work of Robert Keehn of the National Research Council's Medical Follow-up Agency, which had primary responsibility for conducting a questionnaire survey of test subjects to evaluate aspects of their current health, family status, and lifestyle.

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EXECUTIVE SUMMARY

At the request of the Department of the Army, the Committee on Toxicology in the Board on Toxicology and Environmental Health Hazards of the National Research Council's Commission on Life Sciences undertook a study to investigate possible delayed and long-term effects of experimental chemicals administered to soldiers at the U.S. Army Laboratories, Edgewood, Maryland. A total of 6,720 soldiers volunteered, of whom 4,826 were exposed to some experimental chemicals. The Edgewood tests, conducted over a 20-year period ending in 1975, were intended to investigate the immediate and short-term human-performance effects of short-term exposure to various chemicals with warfare potential and the subjects' responses to therapy for such effects.

Five panels of about 10 scientists each, with appropriate expertise, reviewed the available information on the test chemicals, which were divided into five categories according to pharmacologic class. Available information included reports of acute effects by physician observers and published reports in the scientific literature.

Volume 1 of this series was concerned with the possible long-term effects of 15 anticholinesterase and 24 anticholinergic chemicals and was issued in 1982. Volume 2 was concerned with four cholinesterase reactivators, 12 psychochemicals, mustard gas, and a variety of irritant substances; it was issued in 1984. This report is Volume 3 of the series.

Early in this study, the Committee decided that the information on the test materials would be incomplete if the long-term morbidity and mortality among the test subjects were not investigated. It was recognized that the Edgewood tests were intended for short-term and not long-term study and were therefore deficient in adequate long-term controls. The Committee, recognizing these limitations, nevertheless believed that the study might detect major effects if they were present and that the limitations of the study could be appropriately described so its conclusions would not be overinterpreted. Mortality was reported in Volume 1 and is updated in this volume. Morbidity was analyzed through use of a questionnaire that was sent to all living test subjects whose current addresses could be located and through study of Army and Veterans' Administration (VA) hospital admissions of the participants after testing.

This volume was prepared cooperatively by the Medical Follow-up Agency of the Commission on Life Sciences and a coordinating committee

composed of prior panel chairmen, three epidemiologists who had served on the panels, and one newly selected epidemiologist. The charges to the reporting group were as follows:

- To prepare a final report for the series Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents on the basis of results of a questionnaire regarding current health status of test subjects.

- To evaluate the implications of findings from the questionnaire for any of the conclusions reported in Volumes 1 and 2.

Edgewood test subjects who were alive and could be located received a mailed questionnaire intended to assess their current health status; 82% of those who received the questionnaire responded to it.

The long-term health effects of most interest included the possibility of excess cancer risk and adverse mental, neurologic, hepatic, and reproductive effects that might have resulted from experimental exposure to chemicals at Edgewood.

Subjects tested with anticholinesterase chemicals, anticholinergic chemicals, cholinesterase reactivators, or psychochemicals did not differ significantly from control subjects or from those tested with other classes of drugs in their replies to questions about their current health status. Almost 90% of all these respondents reported no health problems related to the exposures under scrutiny, and 79% reported good to excellent health. (Subjects tested with LSD were not within the purview of the Committee's investigation, because they had been evaluated and reported on earlier by the U.S. Army, whose evaluation was based on physical examinations. Analysis of responses to the Committee's questionnaire did indicate, however, that there was an increased use of LSD after the Edgewood tests, but there was no evidence of adverse health effects among these subjects.)

The subjects tested with irritants and vesicants, including those who developed skin burns from mustard gas, reported no increased prevalence of significant skin cancer or other adverse health effects.

The test subjects' current use of tobacco and alcohol and their histories of use of recreational drugs were not unusual.

When the observed fertility of men exposed to anticholinergic chemicals was compared with age-adjusted expected values, based on the experience of the men who were tested with other chemicals, there appeared to be a decrease in fertility. However, the men who were exposed to anticholinergics were, by and large, tested during the second half of the 20-year testing period. Because of the national trend toward delayed and smaller families, these analyses were further

adjusted for the date of testing. When adjustment for age of volunteer when last tested was performed, there was no difference between the observed fertility pattern of the men exposed to anticholinergic chemicals and that expected on the basis of men who were exposed to other chemicals.

A review of records of admissions to Army hospitals in calendar years 1958-1983 and admissions to VA hospitals in calendar years 1963-1981 produced some interesting findings with regard to Edgewood test subjects: a barely statistically significant increase in admissions to VA hospitals for malignant neoplasms among men exposed to anticholinesterases and statistically significant increases in admissions to VA hospitals and Army hospitals for nervous system and sense organ disorders among men exposed to LSD. However, the numbers of these admissions were small, no dose relationships were noted, and, in the case of anticholinesterase exposures, no clustering of specific chemicals in relation to tumor sites was noted.

The experimental methods and the available comparison groups were such that only large effects were likely to be uncovered. The large standard errors, the initial differences between the exposed and nonexposed groups, the possibility that more than one exposure might have led to the same adverse effect, and the self-reporting nature of the questionnaire study all would tend to obscure small differences.

CONTENTS

INTRODUCTION

This is the third and final volume in a series that reports the findings of five panels of the National Research Council's Committee on Toxicology regarding possible long-term health effects of exposure of volunteers to a variety of experimental chemicals in 1955-1975. All exposures took place at the U.S. Army Laboratories (formerly Army Chemical Center), Edgewood, Maryland.

The work of the panels began in 1980, when the Department of the Army asked the Committee on Toxicology in the Board on Toxicology and Environmental Health Hazards of the National Research Council's Assembly of Life Sciences (now the Commission on Life Sciences) to review the Edgewood experimental studies and advise on the long-term or delayed health effects that the volunteer test subjects might have sustained.

There are two important reasons for conducting these studies, one moral, the other scientific. The first involves the U.S. government's responsibility to its soldier test subjects to learn whether its investigations have resulted in delayed or long-term adverse health effects. The second involves curiosity in the wake of experiences with new chemical entities that resulted in unanticipated problems, such as the sulfanilamide disaster of 1938, the thalidomide episode of 1963, and the genital tract effects of diethylstilbestrol (DES); all those contributed to a Food and Drug Administration requirement that new drugs be monitored, especially during the first months of marketing. One excellent example of the benefits of careful postmarketing surveillance is the PUVA (psoralen-ultraviolet light therapy for psoriasis) program conducted by dermatologists. This led to identification of a qualitative and quantitative carcinogenic potential of PUVA.

In 1982, the Committee reported (Volume 1)[9] on possible long-term health effects of two pharmacologic classes of chemicals tested at Edgewood: 15 anticholinesterase chemicals and 24 anticholinergic chemicals that had been administered to some 3,200 subjects. Two panels, each consisting of about 10 scientists in various disciplines, provided the main framework for the report. In 1984, the Committee reported (Volume 2)[10] on three other pharmacologic classes of chemicals: four cholinesterase reactivators, administered to approximately 775 subjects; 12 psychochemicals, administered to approximately 288 subjects; 98 irritants, administered to almost 2,000 subjects; and mustard gas, administered to 152 subjects. Three panels of scientists were involved in that work. Summaries of the two earlier reports are presented in Appendix A.

A questionnaire was sent to the test participants in 1984 to learn about their current health status. A coordinating committee reviewed the findings of the questionnaire and had two charges:

- To prepare a final report for the series Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents on the basis of results of the questionnaire.

- To evaluate the implications of findings from the questionnaire for any of the conclusions reported in Volumes 1 and 2.

This volume focuses on the analysis of results of the questionnaire. It also updates the analysis of deaths among the subjects after testing (reported in Volume 1) to include 1,454 tests unavailable at the time of the earlier work (see Appendix B). The numbers of volunteers did not change, but the numbers of tests performed, and hence the numbers of chemicals and possibly chemical groups to which the men were exposed were increased, because additional information was available. The new material did not change the original findings concerning deaths; no excess of mortality appeared among subjects tested with the five classes of chemicals or with LSD, which was the subject of a separate report.[14]

Some 6,720 volunteers participated in the Army tests. For 325 of these, a claim for burial allowance had been received by the Veterans' Administration by 1984, leaving 6,395 presumed to be still living. Of these, 1,399 were lost because current mailing addresses could not be obtained, owing to the absence or inaccuracy of personal information available from Army records. It is not known whether this could be a serious source of bias in the comparison of treatment groups. The 911 men who received the questionnaire and failed to respond were considered to constitute another potential source of bias, inasmuch as their failure to respond could have resulted from an unhappy test experience. Because the Army was interested in learning more about soldiers who did not respond to the questionnaire, a subcontract was arranged with the Research Triangle Institute, Research Triangle Park, North Carolina, to find out why some men failed to respond. The findings are summarized in this report.

Development of a single questionnaire suitable to the needs of five panels of about 50 scientists working with five pharmacologic classes of chemicals administered to different numbers of subjects proved to be a formidable task. The concerns and difficulties encountered are discussed in Appendix C.

THE MEDICAL FOLLOW-UP STUDY

Men who are selected to serve in the Army are, in general, in better physical and mental health than their peers. Because their later health would also be expected to be better than average, it is inappropriate to compare their health and life experiences with those of the general U.S. male population. One option for this report would be a purely descriptive presentation of the findings derived from hospital records and a questionnaire. But the men exposed to the various chemicals differed in several ways, such as in age and date of testing, so a simple presentation of outcomes could be misleading. To permit useful conclusions to be drawn about the experience of men in the different chemical-group tests, comparative statistics were developed on the basis of observed and expected life experiences of comparison groups.

ANALYTIC PROBLEMS

The testing of chemical agents in human subjects at Edgewood began in 1955 and continued for some 20 years. The main objective of these tests was to determine effects of various chemical agents on the ability of test subjects to function effectively in a military situation. It was not anticipated that any late effects would occur. In fact, two characteristics of the testing program make the demonstration of late effects extremely difficult:

- Selection Bias: The volunteers received careful physical and mental screening examinations for contraindications to the planned tests. The health of a volunteer helped to determine the type of test in which he participated. The more healthy men were exposed to the active chemicals, and the less healthy were used as controls and in some cases tested equipment without being exposed to chemicals. Such selection bias means that the men not exposed to chemicals would be expected to have more illness; therefore, the likelihood of discovering effects in them (whether early or late) due to the treatments would be smaller.

- Multiplicity of Chemical Exposures: For the sake of efficiency, many volunteers were used in two or more tests. If a test substance produced detectable long-term adverse effects in a man who was also exposed to another substance, it could be difficult to ascribe the effect to the first substance alone, especially if many men were tested with both substances.

The Committee had many discussions on how best to evaluate the effects of the test chemicals, given the lack of suitable control populations and the multiple exposures of some of the men. It was decided that two comparison groups would be used. The first group included the subjects who received no test chemicals--the "no-chemical-test" (NCT) group. Although these men met the requirements for military service, they did not meet the rigorous standards demanded for exposure to chemicals. A second comparison group consisted of subjects who were tested with chemicals other than those being evaluated in a particular statistical comparison--the "other-chemical-test" (OCT) group. Suggestions to use additional comparison groups from other populations as surrogate controls were quickly turned aside, because the factors involved in selecting subjects for the Edgewood tests were not well understood and would involve variables that were not available for analysis, such as race, religion, socioeconomic status and characteristics related to subjects' desire to volunteer for the tests.

Several other problems that make simple comparisons between exposed and unexposed groups difficult are discussed below.

DIFFERENCES IN AGE AT FOLLOW-UP

Posttest experiences of groups of volunteers cannot be compared solely by comparing numbers of events experienced; one must also take age differences among the test groups into account. Volunteers in the early test years were about the same age at the time of testing as men tested later (Table 1). By 1984, the participants in the early tests had a much longer posttest period than the most recent participants; men tested more recently are younger now than men tested earlier. Thus, those tested earlier are more likely to have had experiences that are more frequent with advancing age, even in the absence of exposure.

The testing program spanned a period of some 20 years, and the chemical agents tested changed with time (Table 2). For example, the testing of LSD derivatives was concentrated in the early years; more than half the doses had been administered by the end of 1959. At the other end of the testing period were tests of FDA-approved drugs, innocuous chemicals, and control substances. One can therefore expect health problems more common to the later years of life to have occurred in a much higher proportion of men in the LSD tests than of men who received approved drugs, innocuous chemicals, or control substances, even if LSD and its derivatives do not promote such health problems.

Because of the age differences, comparisons between groups were adjusted for current age.

MAGNITUDE OF DETECTABLE EFFECTS OF CHEMICAL EXPOSURES

How small a real effect can one reasonably expect to detect? The answer to this question depends on several factors:

- The number of subjects exposed to each chemical of interest. This number is fixed for each chemical tested.

- The number of subjects available for comparison purposes.

- The proportion of members of each chemical-test group and comparison groups on whom follow-up information is obtained.

- The level of significance at which the null hypothesis of "no effect" will be rejected. The 5% level is proposed for screening purposes. For this kind of examination, a one-sided test of significance, directed solely at identifying adverse exposure effects, is appropriate. (In making such a test of significance, it is assumed that the chemical-test participants have not benefited from their exposure.)

- The "power" of a study is the probability that a true effect of a given size, or larger, will be detected in that study and labeled "statistically significant." "Power" depends on how big the true difference is (or is expected to be) and how many persons there are in the exposed group and the comparison group. The larger the true difference, the more likely it is to be detected, hence the greater the power. Similarly, the larger the number of persons observed, the more likely that a given difference will be found to be statistically significant. In general, bigger true difference and larger study both mean greater power.

Power calculations are shown in Tables 3 and 4 for comparison with two base line groups of participants: the NCT group, consisting of subjects who did not participate in any of the chemical tests (those exposed only to FDA-approved drugs or placebo substances and those who were exposed only to equipment); and the OCT group, consisting of subjects who were not exposed to a chemical of interest, but were exposed to other test chemicals. Like use of the NCT group, use of the OCT group can decrease the probability of detecting effects of exposure to specific chemicals. In both comparison groups, health status, including fertility, might be lower than in a true control population. That could be the case in the NCT group because the selection process included volunteers who were less healthy. It could be the case in the OCT group if exposure to chemicals other than those of interest in a particular test had independent health effects on those volunteers.

Table 3 summarizes power calculations based on 1,058 men in the NCT group who responded to the questionnaire (discussed later), and

Table 4 summarizes power calculations based on a typical number of respondents in the OCT group.

As an example of how to use these tables, assume that 1,000 exposed respondents are being compared with the 1,058 NCT respondents (Table 3). Assume further that the background, or base line, risk among the comparison subjects is 10% (0.100) and that we wish to discover the true effect of exposure that results in an additional 1% (0.010) above the background risk (the resulting risk in exposed subjects is therefore 11%). For 1,000 exposed (the NCT comparison group), the intersection of the column representing the 10% base line risk and the row representing a 1% risk increase due to exposure contains the value 0.183, which signifies that there is an 18.3% chance of reporting a significant increase among exposed respondents.

Table 4 is computed in the same manner as Table 3; however, the size of the OCT comparison group is not constant, but increases as the exposed group decreases, and by the same amount.

Tables 3 and 4 show that the probability of observing a significant difference decreases with reduced numbers of exposed respondents and with an increased base line risk. As might be expected, the larger the true increase in risk, the larger the probability that the increase will be detected and labeled statistically significant.

MULTIPLE COMPARISONS

Tests of statistical significance lead to statements concerning the probability that some observed difference could have been due to chance alone. Probabilities are computed as though only one significance test, or comparison, had been conducted. However, one is seldom faced with a single-comparison situation. As the number of comparisons increases, so does the probability that chance alone will lead to finding "significant" differences.

In this report, the five chemical classes were analyzed separately as seven groups; the psychochemical class was analyzed separately for those exposed to LSD, Sernyl, and cannabinoids. Furthermore, the data on the men who were exposed to chemicals of only one class were analyzed separately from the data on those exposed to chemicals of that class and later to chemicals of another class. Therefore, in the following analyses, 14 chemical-test groups (seven with single chemical-class exposures and seven with multiple chemical-class exposures) are compared with two baseline groups on at least 27 end points (outcomes), for a minimum of 756 comparisons (14 x 2 x 27 = 756). In the absence of any real adverse chemical-test effect, it is to be expected that several differences will be declared "significant" at the 0.01 level, and possibly even one at the 0.001 level, assuming that the end points are independent. Collateral data must therefore be brought to bear before even findings that are statistically highly

significant (i.e., $p < 0.001$) can be said to demonstrate that a true effect exists. Some of these collateral data are based on determination of whether a dose-response relationship exists, whether the association is biologically reasonable, and whether the effect can be explained by peculiarities in or differences between the comparison populations.

METHODS OF STUDY

This report is based on a follow-up of the 6,720 men who participated in experiments conducted by the Army at the Aberdeen Proving Ground, Edgewood, Maryland, in 1955-1975. Follow-up information was obtained from four sources:

- A tape file, provided by the Army, of admissions of participants to Army hospitals during calendar years 1958-1983. This file made possible the examination of the hospital experiences of volunteers between the time of test participation and separation from the service.

- A tape file, provided by the Veterans' Administration (VA), of admissions of participants to VA hospitals from 1963 to 1981. This file was used to examine the use of VA hospital facilities after separation from the service.

- Responses to a health questionnaire mailed to men who were still living in 1984.

- Information obtained from men who initially did not respond to the questionnaire, but provided interviews when asked to do so in follow-up telephone calls.

OBTAINING ADDRESSES

The mail survey of health status was undertaken to obtain information related to health, social adjustment, and lifestyle during the posttest period. The survey was directed at 6,395 men for whom no claim for a burial allowance had been received by VA (Table 5). Several sources of address information were used, including the VA compensation and pension files, records at the St. Louis Military Personnel Records Center, the National Institute for Occupational Safety and Health (which can obtain current address information from the Internal Revenue Service on persons with occupational exposure to possible health risks), and a commercial tracing agency. Addresses of 5,620 volunteers, or 88% of those not known to be dead, were obtained. Of these addresses, 624 (11%) were reported by the U.S. Postal Service to be incorrect, leaving 4,996 persons who are believed to have received the questionnaire; of these, 4,085 responded. The information on the total group of volunteers participating in the Edgewood studies follows:

	No.	%
Total participants	6,720	100.0
Died before survey	325	4.8
Could not be located	1,399	20.8
Located, but failed to respond	911	13.6
Located and responded	4,085	60.8

Table 5 shows the follow-up information on the persons in each chemical-test group. Presumably correct addresses were obtained for 4,996 men, or 78% of all living volunteers; this varied from 70% of men used in tests of LSD to 84% of those used in tests of the anticholinergics and cholinesterase reactivators. There was substantial uniformity from test group to test group in the proportion of persons responding to the questionnaire, once the participants were located. The response rate, 82% of all participants, was slightly higher among the participants in the chemical tests (81-84%) than among the NCT group (78%).

The likelihood of obtaining an address for a volunteer was greatest for those who participated in the most recent tests and decreased as the time since test participation increased (Table 6). Valid current addresses were obtained for 83% of living men involved in tests conducted in 1970 or later, compared with 81% of men who participated in 1960-1964. For the men involved during the earliest years, before the replacement of the Army Service Number with the Social Security Number, the address yield fell to 57%. Knowledge of a person's Social Security Number is very important for successful tracing. The Internal Revenue Service failed to locate in its files only 171 (3%) of the 5,680 men whose Social Security Numbers were sent for tracing (Table 7). The earliest test groups, Sernyl and LSD, had the highest proportions of "no record of SSN" responses; however, IRS still found in its files more than 95% of the persons whose Social Security Numbers were known. The proportionate yield of good addresses of the living among the various chemical-test groups varied from 70% for LSD-tested subjects (early tests) to 84% of men exposed to anticholinergic chemicals (recent tests), as shown in Table 5. Addresses were obtained for 76% of living subjects in the several test categories that constitute the NCT comparison group.

CONTACTING BY MAIL

Up to three mailings, 6 weeks apart, were made to a man at a given address. The first mailing contained the questionnaire and an explanatory letter (Appendix E, Exhibit A). The second and third mailings included supplemental letters (Appendix E, Exhibits B and C) emphasizing the importance of a reply. An addressed, postage-paid envelope was enclosed with each mailing. The third mailing to a given address was sent by certified mail with return receipt requested as proof of delivery, and the enclosed letter invited the man to telephone the study director, reversing the charges, if he wished to inquire further concerning the survey. A mailgram (Appendix E, Exhibit D) was sent at

the time of the third mailing, advising the subject that the third request was on its way, in the hope of convincing him that the letter should not be treated as discardable mail. The mailing sequence ended on receipt of a completed questionnaire or a refusal. If the Postal Service returned a letter marked "address incorrect," another mailing sequence, to the next most likely address on file, was started. The priority for the use of addresses was (1) that obtained from the IRS, (2) that obtained from the VA compensation and pension file, (3) that obtained from service records, and (4) commercial tracing.

The cutoff date for receipt of questionnaires to be included in the analysis was February 1, 1985. Questionnaires were received from 4,085 men, 64% of survivors (Table 8). The response rate for men who were correctly located was 82%; 2% of located men declared their unwillingness to participate, and 16% of those located failed to respond. Those who failed to respond were telephoned, and when necessary visited, to determine the reasons for their not responding.* A total of 657 (74%) of the 891 nonrespondents were interviewed. The results of the interviews are discussed later.

COMPARISON GROUPS

The chemical tests were conducted by the Army for the sole purpose of studying immediate effects. The tests in which a volunteer participated were therefore determined by the tests being conducted at a given time. Volunteers participated in an average of 3.3 tests. Some were tested more than once with the same material, and some were tested with several materials. Only 43% of respondents in any chemical-test group were exposed to only a single class of chemicals. That is, most of the men were exposed to multiple chemicals from different chemical groups. Thus, comparisons of importance to the search for late effects
are those between men who participated in tests involving a single class of chemicals and the 1,058 volunteers in the NCT comparison group. The NCT group includes:

- 907 respondents who were not exposed to drugs (used mostly in tests of equipment).
- 93 respondents who were exposed to FDA-approved drugs (58 different).
- 17 respondents who were exposed to relatively innocuous substances (alcohol, caffeine, etc.).
- 39 respondents who were exposed to control substances (water, saline, bicarbonate of soda).
- 2 respondents who were exposed to two of the above.

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* This survey of nonrespondents was conducted by the Research Triangle Institute, Research Triangle Park, N.C. 27709.

Evidence that the NCT group was composed of the less healthy volunteers dictated that other comparison groups be defined--groups less likely to have a built-in health bias. These groups, the OCT groups, consisted of all volunteers who participated in chemical tests other than those under immediate evaluation. Members of the OCT groups had received one or more of the chemicals. By definition, the OCT groups were likely to yield underestimates of possible effects of exposure to specific chemicals, because its members were exposed to other chemicals. Although the possibility of adverse effects due to other exposures must be considered, no such effects were noted when the OCT groups were compared.

Table 9 is a sample of the computer tables used in the preliminary screening of the data. Multiple test-group comparisons (described below) were considered in deciding whether a given category of chemical appeared to have had an adverse effect on exposed volunteers. The categories shown in Table 9 are those used in the study of men exposed to anticholinesterase chemicals. Similar groups were defined for the other categories of chemicals. The column definitions are as follows:

- A ALN (Alone): Persons who participated in tests of the category of chemical named in the table heading and no others (in this example, the anticholinesterases).

- A AND: Persons who participated in tests of the category named and in tests of at least one other category.

- TTL A: The sum of A ALN and A AND (i.e., all persons exposed to the category named).

- CNTRL: The no-chemical-test (NCT) comparison group defined earlier.

- OTHER: All subjects in chemical tests except those involving the category named, i.e., the other-chemical-test (OCT) comparison group.

- NOT A: All subjects (including the NCT group) minus volunteers who participated in tests involving the named category (i.e., the sum of CNTRL and OTHER).

- TOTAL: All respondents (i.e., the sum of TTL A and NOT A).

Each computer table consists of several panels representing current age categories in 1984 (the survey year) and a "total" panel representing the sum of all age groups. The responses to the various questions of the questionnaire are defined by the labels in the left margin. Table 9 deals with whether the volunteers requested information about the results of the study. The percentages are based on column totals for a given panel.

Whether a class of chemicals might have had an adverse effect on exposed subjects was based first on inspection of the percentages of subjects with similar responses in each of the first five columns named above. This inspection was performed separately for each age group. If it appeared that the responses of those who were exposed to the chemical group of interest alone or in combination differed from the responses of the NCT group (control) or the OCT comparison group (other), the pooled data were compared with a more rigorous analysis that included adjustment for age differences and testing for statistical significance. Age was adjusted for by calculating the expected number of the given response for each age group. Expected numbers were based on the proportion of NCT subjects who responded in similar fashion. This proportion was then multiplied by the number of subjects in the exposed group to find the expected number of the given response for that age group. The expected numbers were then summed for all age groups to get a total expected number, which was compared with the total observed number of responses. A similar adjustment was made with the OCT comparison group.

For assessment of fertility and other relevant variables, current marital status was also adjusted for. In these cases, the data were adjusted for age and marital status concurrently. That is, the population was divided into age groups, which in turn were divided into marital-status groups for purposes of determining expected values.

Significance testing was performed with observed data for both the exposed and comparison groups. Each group was subdivided into age-specific groups, and the Mantel-Haenszel chi-square test procedure was used.[6] This procedure tests for differences between exposed and comparison groups by combining tests performed for each age group. For this purpose, the responses were reclassified in some cases into only two categories, i.e., dichotomized. For example, the total number of children of each man was reclassified into no children and at least one child.

In some instances, particularly with respect to occurrence of specific disorders, the total numbers of events were very small. For these comparisons, a Fisher exact test was used to generate the probability of observing the number of events actually reported by the respondents, given the numbers observed in each of the two comparison groups. For example, assume that 10 of the respondents reported a particular disability, including 4 exposed subjects and 6 who were not exposed. The exact test provides the probability that the 10 reported events would include 4 or more exposed subjects (an excess as great as or greater than that observed).

The response of interest in Table 9 is whether the volunteers asked to be informed about the results of the study. It is apparent that more men who were involved in tests of anticholinesterases asked to be informed of the results of the studies than NCT subjects. Of all the groups studied, the NCT group showed the least interest in the results.

RESULTS

A total of 27 outcome variables (Table 10) related to the health, social adjustment, and reproductive experiences of the Edgewood participants were examined for each of the seven classes of chemicals tested. That led to 189 possible decisions concerning the existence of a chemical effect--27 decisions for each of the seven chemical groups. Only a few of these decisions were judged to have possibly a significant association between exposure and the outcome variable. The evidence leading to those judgments is presented in this chapter. In addition, detailed comparisons were made where there was some biologic reason to anticipate a specific response, even though preliminary examination of the data did not suggest an effect.

ADMISSIONS TO HOSPITALS

Admissions to Army Hospitals

The Army provided a tape file of admissions of volunteers to Army hospitals in calendar years 1958-1983. This file does not cover the early test years, but the loss of information is limited to the early posttest years and to men who participated during the first 3 years of Army testing. The numbers of volunteers under observation during each posttest year were counted for each of the chemical groups of volunteers; separation from the service terminated observation.[3] Follow-up of volunteers began at the time of testing, or in 1958 for those tested earlier, and numbers of person-years of observation were summed over successive posttest intervals. Rates of hospital admissions were estimated per 1,000 person-years of observation. Percentages of men hospitalized were based on the mean numbers of men being followed.

Army hospital admission rates after test participation are shown separately for men exposed to a single class of chemicals (Table 11) and for men exposed to more than one class of chemicals at Edgewood (Table 12); the two groups are mutually exclusive. These data, and those on the VA hospital admissions that follow, are reported for all volunteers, not only those who returned the questionnaire. For each class of volunteers, the need for Army hospital admission was greatest during the first 5 years of follow-up and decreased over succeeding intervals. However, neither table shows that the men in any of the chemical-exposure groups appear to have had more hospital care than did the NCT group.

Hospital admission rates were more sensitive to the frequency of hospital care than were the percentages of men hospitalized. Numbers of men admitted to Army hospitals were compared for men exposed to only one chemical group (Table 13) and for men exposed to chemicals in more than one group, including the group of interest (Table 14). The percentages of hospitalized men in each chemical-test group seldom exceeded that of NCT subjects more than trivially. No pattern of

excess hospital use was shown for any chemical group when the one-class and multiple-class exposure groups were compared.

The medical conditions responsible for admissions were examined in broad categories based on the Eighth Revision International Classification of Diseases (1967-1969),[26] referred to as ICD 8. Among the more frequently encountered diagnostic categories for all volunteers are respiratory disease (359 admissions, 16.1% of total), digestive disorders (260, 11.7%), infectious and parasitic diseases (202, 9.1%), musculoskeletal and connective tissue problems (178, 8.0%), and symptoms, ICD 8, codes 780-796 (162, 7.3%). These five categories account for over half the 2,231 recorded Army hospital admissions of these volunteers since testing. Furthermore, these medical conditions are common in Army life. Conditions that might have resulted from the various chemical exposures resulted in few admissions, with rates similar to those for the NCT subjects. The medical conditions that might have resulted from exposures include malignant neoplasms; benign and unspecified neoplasms; endocrine, nutritional, and metabolic diseases; diseases of the blood and blood-forming organs; mental disorders; diseases of the nervous system and sense organs; and diseases of the circulatory system. Several of these groups of disorders are examined separately below.

Admissions to VA Hospitals

Data on admissions to VA hospitals have been obtained from the VA for the years 1963-1981. Because only 15% of veterans' hospital-care needs are provided by VA,[1] the rates of postseparation admission of men exposed to a single chemical group (Table 15) and to more than one group (Table 16) grossly underestimate hospital use by these participants. However, there is no a priori reason to suspect that those exposed to one chemical group are more likely to depend on VA for their hospital needs than another group. Thus, the rates shown for the several chemical groups are assumed to be comparable.

Admission rates for various postseparation intervals show considerable variation between chemical groups. Although there are exceptions, the NCT subjects generally experienced the highest admission rates. This relationship is seen clearly when the postseparation period is examined as one unit. The procedures used by the Army to select NCT subjects apparently had the effect of identifying, on the average, men more likely to use or require hospital care after discharge.

In Table 16, the exposure group with the highest admission rate is the Sernyl group, but comparison with Table 15 shows that 38 of the 39 admissions were of men exposed to other chemicals, as well as Sernyl. The admission rate among those exposed to several chemicals including Sernyl was 57.0 per 1,000 person-years. However, because the total number of men, and consequently of person-years of observation, is so

small for this group, the increase could easily be due to chance, rather than to exposure to Sernyl. Most of the increase occurred 5-14 years after exposure to the chemicals.

Admissions for Selected Disorders

Hospital admission rates constitute a good index of the need of the test participants for hospital care, but they can be distorted by the repeated admission of a few persons for a given condition. This problem can be eliminated by examining the numbers of men admitted to hospitals for selected conditions. Three categories of illness of particular interest for possible relationship with the chemical agents tested are malignant neoplasms (ICD-8, codes 140-239). mental disorders (ICD-8, codes 290-315), and diseases of the nervous system and sense organs (ICD-8, codes 320-389). The numbers of men admitted to Army hospitals and to VA hospitals for these conditions for each chemical-test group are shown in Tables 17, 18, and 19. Two counts of "expected" admissions are also shown: those based on the experience of participants exposed to chemicals other than the group being considered for a specific comparison, the OCT group; and those based on the NCT group experience.

Seven volunteers were admitted to Army hospitals for malignant neoplasms during their posttest period of service, of whom three were NCT subjects and four were participants in chemical tests (Table 17). Chemical-test participants as a group experienced fewer admissions than were expected on the basis of the NCT experience. When each chemical-test group was compared with all other groups combined, the differences between observed and expected admissions for malignant neoplasm were in general no greater than might be expected owing to chance. All six cases of malignant neoplasms treated in VA hospitals, however, occurred among participants in chemical tests. Three chemical-test groups had more cases than expected: anticholinesterases, anticholinergics, and cholinesterase reactivators. There is duplication among the cases associated with these three groups, because some of the subjects had been exposed to more than one chemical. Hence, the sum, nine admissions, is greater than the six admissions to VA hospitals. The number of neoplasms among the anticholinesterase-exposed men was not significantly increased over the OCT expected number. When an exact test was performed with the four cases in the anticholinesterase group and no cases in the NCT group, the results were barely significant. An examination of the admission diagnoses revealed no consistent pattern of site involvement. There were two cases of cancer of the trachea or lung; one each of cancer of the lip, skin, and lymphoid tissues; and one myeloma.

Mental disorders (Table 18) led to admission of 56 participants to Army hospitals and 109 participants to VA hospitals after separation. Both the Army and the VA experiences clearly indicate that NCT subjects were more likely to have mental disorders requiring hospitalization

than were the chemical-test participants and indicates that this group was not as fit as those who were given experimental chemicals. Because of the increased frequency of mental disorders among the NCT group, a more useful comparison for the chemical groups is obtained by using men tested with other chemicals to compute expected values. For no specific chemical group were more men admitted to Army or VA hospitals than expected on the basis of the NCT comparison group. In comparison with expectation that was computed from the OCT comparison group, there were slight excesses in four of 14 categories, but in no case was the excess statistically significant.

Diseases of the nervous system and sense organs resulted in the admission of 43 participants to Army hospitals and 16 to VA hospitals (Table 19). Consistently more chemical-test participants were hospitalized for diseases of the nervous system than would be expected from the NCT experience, both while in the Army and after separation. The numbers of admissions for these disorders were significantly higher than three of the four expected values for the men exposed to LSD. Among the LSD-exposed volunteers, three were hospitalized for otitis media, two for diseases of the retina (not detachments), one for a cataract, and one for deafness. No Sernyl participants were admitted for this group of illnesses; Sernyl-exposed men constituted the only group with fewer participants admitted than expected on the basis of the NCT experience. Half the men admitted to Army hospitals for diseases of the nervous system and sense organs were first admitted within 5 years of testing, whether they were in chemical-test groups or the NCT group. When the distributions of specific diagnoses are compared among the test groups, no consistent pattern is seen that suggests that any of them can be attributed to the testing program.

MAIL SURVEY

Response Bias

As noted earlier (Table 5), responses were received from 4,085 participants--64% of the 6,395 men who were believed to be living when the mail survey was conducted and 82% of the 4,996 men who were located. Because responses to the questionnaire survey were not obtained from all living men, it is necessary to compare the health of respondents with the health of those who were located but did not respond and of those who could not be located. The current health status of the three groups could not be evaluated directly, but it has been possible to examine the percentages of men still in the Army at successive intervals since testing and the percentages that were hospitalized during each interval (Table 20). The upper panel of Table 20 shows the mean annual numbers of men who were still in the service during successive 5-year posttest intervals. The center panel shows the numbers of these men who were hospitalized by the Army, and the lower panel shows the percentages of hospitalized men among those still in service.

The overall use of hospitals was highest during the 5-year period immediately after test participation. The proportion of participants hospitalized beyond the fifth posttest year was greatest among men who responded to the questionnaire, somewhat lower among men who failed to respond, and lowest among men who could not be located. These percentages suggest that men who could be the most likely to have health problems were most likely to respond. If a response bias exists, therefore, it is in the direction of overestimation of current health problems of the living volunteers.

Survey of Nonrespondents

An attempt was made to interview the current nonrespondents (in person or by telephone) to answer four basic questions:

- Did the man participate in the Edgewood testing program?
- If so, did he receive any of the mailings addressed to him?
- If so, did he respond to the questionnaire?
- If not, why not?

An arrangement was made with Research Triangle Institute (RTI), Research Triangle Park, North Carolina, to attempt to interview the 891 men who had not responded (20 of the nonrespondents were not identified in time to be included in the survey). The survey instrument used is shown in Exhibit E of Appendix E.

Interviews were obtained with 657 nonrespondents, 74% of the total (Table 21). The proportion of men interviewed from among the chemical-test groups varied from 71% for the irritant or vesicant group to 91% for the Sernyl group. Thirty-six nonrespondents (4%) refused to be interviewed--from none of the Sernyl group to 7% of the LSD group. RTI was unable to contact the remaining 198 (22%) of the nonrespondents (from 9% of the Sernyl group to 24% of the anticholinesterase group and irritant and vesicant group). These 198 included 74 participants who could not be located.

The identification of participants among the nonrespondents was reasonably good; 643 (98%) of persons interviewed confirmed their having been on special assignment to the Aberdeen Proving Ground. Of the 643, 102 (16%) could not recall having received any of the three mailings (Table 22). It is reasonably certain that the third letter was delivered, inasmuch as certified-mail receipts of delivery were returned for the nonrespondents. The letters probably were simply discarded after receipt.

Of the 541 participants who remembered receiving the questionnaire, 62 (11%) claimed to have completed and returned it (Table 23). Only 13

questionnaires were eventually received from these 62 men, including seven received after the cutoff (February 1, 1985). The three most frequently reported reasons for not responding were lack of health problems to report (337 participants, 62%), concern about confidentiality (135, 25%), and judgment that the questionnaire was too personal (114, 21%). There is no evidence that the men exposed to different chemical groups differed in their reasons for not responding, particularly where current health was concerned.

Mail Survey Findings

Age of Respondents. Although the ages of participants at the time of testing were similar among the exposed to the various chemical groups (Table 2), differences in the periods during which the different classes of chemicals were being tested are reflected in the ages of questionnaire respondents in 1984 (Table 24). The mean age of the respondents in 1984 was 42.4 years, with a 9-year spread between the anticholinergic test group (mean age, 40.4 years) and the Sernyl test group (mean age, 49.1 years).

Education of Respondents. The level of education of respondents varied little among those exposed to the various chemical groups (Table 25). Median reported years of education, 13.3 for all respondents, ranged from 12.7 years for the Sernyl group to 13.7 years for the anticholinergic group; 2% of respondents failed to report their education.

Family Relationships. Social status, living habits, and family composition of the various test groups were similar to those of both comparison groups. With one exception, the small observed differences disappeared when the results were adjusted for current age. The exception involves the reproductive experience of men who participated in tests of anticholinergics. Volunteers exposed only to anticholinergics and volunteers exposed to anticholinergics and other chemicals both reported having had significantly fewer liveborn children (stillbirths were not reported) after test exposure.

In comparisons of numbers of children, men who did not respond to the question on children were assumed to have had no children. Most men who failed to respond to this item had never been married. Table 26 shows the numbers of children reported by men tested only with anticholinergics and with anticholinergics and other chemicals. The deficits in numbers of children of those exposed only to anticholinergics and those exposed to anticholinergics and other chemicals were the same: 1.81 children per respondent compared with an expectation of 2.01 children per respondent, based on the age-specific NCT-group reproduction rates. The expected number of men with given family sizes was also estimated on the basis of the age-specific reproduction

histories of the participants in tests of all other chemical groups--a mean of 1.95 offspring were expected per respondent. The deficiency of offspring among the anticholinergic test subjects increased when allowance was made for differences in current marital status (Table 27). However, data were not available to control for duration of marriage after exposure. Allowance for age and education differences reduced the expectation to 1.93 children. An examination of the ratios of observed to expected numbers of men indicates that the anticholinergic-test subjects were less likely to report larger families (three or more children) than were the OCT subjects.

The above analyses were performed with the total family sizes of the men, i.e., including children born before and born after the chemical tests. Approximately 16% of the children were born before testing or within a year after testing. Later analyses therefore used only children born later than a year after exposure. To estimate expected values, the rates were corrected for the ages of the men at the time of testing. That is, a man aged 20 at the time of testing could be expected to have more children born after testing than a man who was 35 at the time of testing. This would be true even if their current ages were the same.

The anticholinergics (median year of testing, 1968) were among the chemicals more recently tested (see Table 2). Because the mean ages of the men at testing were approximately the same for each chemical group, the current mean age of the anticholinergic-test group was the lowest (see Table 24). There has been a general trend in the U.S. population toward lower birth rates and higher ages at conception.[15] Therefore, the apparent decrease in fertility could reflect this trend. Adjusting for the age of the respondent at time of testing does not adjust for such trends. The expected values presented in Table 28 are adjusted for age of respondents at time of testing and year during which the last testing was conducted. With these adjustments, the differences between observed and expected fertilities were sharply reduced when the OCT group was used as the comparison group. However, a deficit in the number of male children born after testing did not disappear after the corrections. When the NCT group was used as the comparison group, the findings were similar, i.e., no significant overall fertility difference and the deficit in number of male births remained significant (see Appendix D). Other information that might be related to the fertility of these men--duration of marriage after exposure, use of oral contraceptives, race, and socioeconomic status, etc.--was not available.

A telephone survey of 50 fathers who reported having had three to five children was made to determine whether reporting had been accurate or whether men with large families underreported family size. Two additional liveborn children were discovered by the survey; a boy "pronounced dead at birth" and a girl born before test participation and therefore intentionally omitted from the questionnaire by the respondent. Six of the 163 reported children, two boys and four

girls, lived only a few hours. Thus, the telephone survey strongly supported the conclusion that the reporting of liveborn children was accurate.

Sex of First Child. The sexes of all the children born to the volunteers exposed to anticholinergics and the children born to the OCT group are shown in Table 28. There appears to be a decrease in male children born to the anticholinergic group. However, to evaluate the impact of an exposure on the sex of liveborn children, it is believed more appropriate to consider only the first child conceived by the volunteer after exposure, hereafter referred to as the first postexposure child. These are the first children born at least 1 year after exposure. If an effect exists, it should be strongest in the first postexposure child. Restricting these comparisons to the first postexposure child born within a given period after the test--say, 1 or 2 years--would have yielded too few children for useful comparisons. A further reason for considering the first postexposure child, rather than all postexposure children, is that some epidemiologists feel that cultural and societal expectations might influence the proportion of children who are male in a completed family. (However, a mathematical modeling of this phenomenon shows that it would have only a minor effect.)

Among the first postexposure children born to men exposed to anticholinergics, 445 (48.7% ± 1.7%) were males and 469 females. Of the first postexposure children of the OCT group, 714 (49.8% ± 1.3%) were males and 720 females. These values are not significantly different.

Among the first postexposure children of the NCT group, 445 (54.9% ± 1.7%) were males, 370 females. This value is significantly different from both the anticholinergic-exposed group and the OCT comparison group. A national survey found that 51.2% of offspring were males.[13 15] For outcome characteristics, such as health, that are strongly affected by the selection of healthy volunteers at a given time, it is clear that comparing these volunteers with a U.S. male population is inappropriate. However, there is no reason why selection for general health at one time should affect the proportion of later children who are male. Therefore, it is appropriate to compare the NCT comparison group, which received no exposure, with this general population. The NCT has a significantly increased proportion of male children ($p < 0.005$), when compared with the national population. But the OCT group does not differ significantly in this regard. Because there is no a priori reason for the NCT group to differ from the national population, sampling errors might explain this extremely high proportion of males. Therefore, it was concluded that there was no clear indication that exposure to anticholinergics would affect the sex of later offspring in a significant way and that there were no animal or laboratory data to support such a finding.

Respondents' Health. Several questionnaire items were aimed at determining the respondents' health status. These ranged from a simple self-assessment of health on a four-point scale (excellent, good, fair, and poor) to the recording of illnesses requiring medical care over the preceding 5 years, confinements to bed for illness or injury during the preceding month, and impairments limiting ability to work and care for oneself. Responses to these items were strongly related to the respondents' ages, so adjustment for current age was particularly important.

Of the 4,085 respondents, 25% reported their health to be excellent, 54% good, and 17% fair. Only 3% of respondents considered their health poor, and 1% failed to respond. None of the chemical-test groups, either alone or in combination with other groups, differed from either comparison group.

When asked whether they had ever been told by health professionals that health problems they were experiencing were due to exposure to a toxic substance, 316 (7.7%) of the 4,085 respondents answered "yes." Only the men exposed to irritants and vesicants had a response pattern that showed a significant increase over either comparison group (Mantel-Haenszel test of "yes" versus "no" responses, $p = 0.05$). The 538 men exposed to irritants and vesicants alone responded as follows:

Reported health problem due to toxic exposure	Observed		Expected	
	No.	%	No.*	%
No	464	86.2	485.3	90.2
Yes	47	8.7	37.4	7.0
Unknown	27	5.0	15.3	2.8
Total	538		538.0	

* Based on the age-specific no-chemical-test experience.

Much of the difference is due to an increase in "unknown" responses. But a review of the nature of the exposures of the volunteers exposed to irritants and vesicants and of a sample of NCT subjects who responded "yes" to this question clearly indicates that acute effects, mainly erythema and blistering during the immediate posttest period, were responsible for the difference. The irritants-vesicants class of chemicals produced no demonstrable excess of late effects. (Long-term health effects of men who experienced acute erythema and blistering are discussed later.)

Half the respondents reported having sought medical care for a disease or illness during the preceding 5 years. There is no evidence that any of the chemical-test groups experienced an increased use of medical care. The irritants-vesicants group, the only one that differed significantly ($p < 0.05$) from either comparison group, reported a reduction in later use of medical care.

Some 29% of respondents reported having been hospitalized during the preceding 5 years. The test volunteers as a group reported fewer hospital admissions than either comparison group. Hospital admissions of the anticholinergics group were significantly ($p < 0.05$) less than those of NCT subjects.

Bed confinements of 1 day or more during the preceding month were reported by 20% of respondents. The experience reported by chemical-test participants tended to be more favorable than that of the NCT comparison group. None of the test-group differences from either comparison group was statistically significant.

Health problems or impairments prevented 337 (8%) of the respondents from working and limited the type of work engagement for an additional 492 men (12%). One test group, subjects exposed to anticholinergics alone (consisting of 353 men), reported significantly ($p < 0.05$) more men with work limitations, as shown below:

	Observed		Expected (NCT group)	
Ability to work	No.	%	No.	%
No limitations	259	73.4	279.7	79.2
Limits work	50	14.2	38.2	10.8
Prevents work	33	9.3	27.1	7.7
Unknown	11	3.1	8.0	2.3
Total	353		353.0	

A review of the responses of anticholinergic-test and NCT men reporting work limitations indicates that no particular type of impairment was involved. Furthermore, there was no difference between the men exposed to anticholinergics and the OCT comparison group. No relationship to specific chemical type, route of administration, or dose was seen. The excess of reported work impairments among men exposed to anticholinergics most likely can be attributed to chance.

Problems in performing household chores were reported by 376 (9%): 159 (4%) reported that performance was "prevented," and 217 (5%) that it was "limited." None of the test groups differed significantly from either comparison group, nor were the directions of differences consistent.

Problems in personal care were reported by eight respondents, and an additional 27 required help with their daily routines. No differences between test groups and either comparison group were noted.

Substance Use and Abuse. Four questions were related to the use and abuse of tobacco, alcoholic beverages, and drugs. Nearly one-third of the respondents never used tobacco regularly. The vast majority of those who smoked on a regular basis were currently smoking cigarettes; 1,493 respondents (37%) smoked at least one pack per day, and 167 cigar smokers and 130 pipe smokers smoked at least one cigar or one pipeful per day. Of the 2,779 respondents who reported ever having smoked regularly (more than occasionally), 1,438 (52%) reported that they no longer smoked. None of the chemical-test groups differed from either comparison group in smoking experience, in terms of the number with a history of regular smoking or current smoking patterns.

The drinking of alcoholic beverages daily was reported by 3,147 (77%) of the respondents; 68% drank beer, 44% wine, and 54% whiskey or other hard liquor. These figures are not different from that reported by adult males in a national survey, i.e., 69%.[15] A total of 231 men (5.7%) reported having had drinking problems that required treatment. Similar drinking experiences were reported by the chemical-test groups and by the NCT group.

Table 29 shows the reported use of selected substances of potential abuse. Most frequently reported was marijuana (37% of respondents), followed by "other narcotics, opiates" (34%), tranquilizers (29%), amphetamines and other stimulants (18%), LSD (12%), barbiturates and other depressants (10%), cocaine (10%), phencyclidine (3%), and heroin (2%).

With one exception, the use of the various substances shows no relationship to chemical-test group. The one exception is the LSD-test group (Table 30). LSD-test subjects reported much more frequent use of the substance than the NCT group or the appropriate OCT group. Most of the excess use of LSD was among those who used it one to nine times, so much of the reported excess might have been due to the reporting of test exposures. However, nine subjects (2.8% of the total) reported having used LSD 10 or more times, compared with 1.2 subjects expected on the basis of the NCT group experience and 2.2 subjects expected on the basis of the OCT group experience. A few of the LSD-test subjects, therefore, appear to have continued to use LSD, inasmuch as no participant received more than four test exposures (or six test exposures, depending on the source of information). Perhaps continued substance abuse by the LSD-test group of soldiers explains in part their somewhat higher rate of questionnaire refusal to respond to the questionnaire for reasons of concern about confidentiality (Table 23).

Groups of Special Interest. The responses of all 38 soldiers who experienced erythema or blisters as a result of exposure to mustard gas were examined in detail, because of the carcinogenic and mutagenic potential of this chemical (see Appendix A). None of the 38 mentioned cancer in response to the question of whether any health professional attributed a health problem to exposure (question 9) or the question of whether any disease or hospitalization had occurred in the preceding 5 years (question 13). One person mentioned cellulitis as a recent health problem, but his physician had not attributed this to the exposure. The mustard-damaged skin site (shoulder) was in a different location from the cellulitis (lower leg).

A second group of special interest consisted of subjects exposed to Sernyl, a purified form of phencyclidine. The primary focus for this group was whether any general health problems or mental disorders had developed as a result of exposure to this chemical. The follow-up responses of 48 men were received; this sample represented 60% of the 80 exposed men who were known to be alive at the time of the survey. In response to the question regarding their "overall health" (question 4), 35 men (73%) reported good to excellent health. The remaining 13 men reported health problems that bore no relation to their test experience in the Army. For example, five men reported "low back pain," three reported "hernias," and three others reported "prostate problems."

No questions were explicitly related to the psychologic status of these men. However, there were only two reports of treatment for alcoholism, infrequent reports of drug use, and no unusual reports regarding employment, marital, and family status. There is no basis to infer above-average frequency or intensity of psychologic problems among these men.

DISCUSSION

In a well-controlled study, subjects are randomly selected for assignment to various test or control groups. In the Edgewood tests, members of short-term control groups were later assigned to test groups and thus were lost as long-term controls. There were two main reasons for this procedure: the Edgewood studies were conducted to determine immediate behavioral effects that might be important in a military situation, and the later exposure of controls to experimental chemicals enabled the experimenter to make multiple use of each volunteer. A need for evaluating long-term health effects was not foreseen.

One might therefore say that this arrangement precludes a proper assessment of long-term effects of the Edgewood tests. Strictly speaking, that is true. However, the present evaluation can support many useful inferences. For example, the lack of excess malignancies among a test population that has received a topical carcinogen would be a significant finding. The lack of excess malignancies and other debilitating diseases in the entire test population would be important. Because of shortcomings in test design, this evaluation is not likely or even intended to reveal minor health deficiencies that might have resulted from the test experience. Only major problems that occur in a large number of men are likely to be uncovered.

The subjects were not assigned to treatments in a formal randomized manner. To be eligible for exposure to the test chemicals, the volunteers had to pass additional physical and mental tests that would have selected the most fit men for chemical testing and the less fit men for testing of equipment and relatively innocuous materials. Nonetheless, two comparison groups could be constructed. The first consisted of the NCT (no-chemical-test) men, and the second, of all men tested with chemicals other than those of interest (the OCT, or ocher-chemical-test, group).

Using the NCT men as a comparison group would tend to underestimate chemical effects, because the NCT men, having been less fit at the outset, might be expected to have more illnesses than the men tested with chemicals. Using the OCT men as a comparison group resolves this problem, but suffers from the possibility that, if more than one chemical led to deleterious effects, we would be comparing one potentially affected group with another potentially affected group. However, because the a priori expectation of the kinds of damage that might be anticipated from each class of chemical would most likely be different, it is unlikely that this kind of loss of information would occur.

Suggestions to use additional comparison groups from other populations as surrogate controls were quickly turned aside because information on the composition of test groups needed to select comparable control groups (race, religion, socioeconomic status) was not available. Furthermore, the effects of the volunteers' desire to participate in the Army studies could not be controlled for.

The Committee has already assessed the possibility of long-term adverse health effects of short-term exposure to the chemical agents tested at Edgewood in two reports (see Appendix A for their executive summaries). The conclusions in those reports were based on a review of literature reporting acute and chronic effects, on the dosages administered to soldiers, and on immediate effects and acute findings reported by clinician observers. The evaluations yielded almost no significant positive findings.

The work reported here involved an evaluation, based on a questionnaire, of the current health status of subjects 10-30 years after testing. The questionnaire asked 15 questions, the most important specifically targeted at learning whether test subjects had experienced higher prevalences of cancer, mental disorders, neurologic disorders, or reproductive effects than members of comparison groups. The results do not indicate that important effects were seen. Answers to questions 4, 9, 11, 13, and 15 a and b were directly pertinent to the current health status of the subjects. The health status of test subjects does not appear to have been significantly altered, according to responses to the questionnaire.

There are several reasons why this study might have low power to detect some long-term effects (see Appendix C). Mail surveys always miss some information and include potential bias; both flaws can result from failure to locate some intended recipients or from failure of recipients to respond. Some questions require the recall of health status or job experience over several years; these kinds of questions often lead to misreporting. Subtle effects on health usually can be assessed only through physical examination and testing. The questionnaire used in this study was largely unvalidated, so its sensitivity and specificity for particular health problems and life quality are unknown. Some attempts at validation were made, however. A subset of volunteers who reported having had three to five children were interviewed by telephone to validate some questions for larger families. But the questions regarding substance abuse and health effects were not validated. Finally, the study had no true control groups. The baseline groups used in this report for comparison, the NCT group and possibly the OCT group, might be expected to have poorer health than a true control group; if that were the case, the probability of detecting some health effects would be decreased. Hence, the objective of this study was to detect major, long-term health effects of the exposures to chemicals.

Additional information on admissions to Army and VA hospitals was available. The data on admissions during the whole period after

exposure were evaluated. The data on Army hospital admissions would give some indication of severe, short-term effects, and the data on VA hospital admissions would provide information on possible severe, long-term effects in men who continued to use the VA system. However, the probability of detecting long-term effects was decreased by the low rate of use of the VA system among men discharged from the service. Again, therefore, the comparisons would detect only major health effects of exposure.

Because so many comparisons (more than 756) were included in this study, it is almost certain that at least one chance difference would be declared "significant" at the 0.01 level. To rule out such chance occurrences, attempts were made to develop corroborating evidence, such as evidence of a dose-response relationship or biologic plausibility. In addition, comparisons were made after controlling or standardizing for known confounding factors.

Another statistical consideration that is relevant to the interpretation of the findings of this study is that the sampling errors are large for the outcomes, because of the nature of the response rates and the nature of the data collected. "Sampling error" refers to the notion that accurate estimation of the range of outcomes requires extremely large numbers of responses. Because many of the groups in this study are small, the ability to detect a true effect (i.e., power) is low. Tables 3 and 4 demonstrat the need for very large populations.

ANTICHOLINESTERASE CHEMICALS

The primary health concern regarding subjects tested with anticholinesterases was that long-term health effects might occur in the form of subtle changes in EEG, sleep pattern, and behavior--such as increased irritability, inability to concentrate and depression--that could persist for more than a year (Appendix A). However, if these changes occurred and persisted, they might be difficult to detect. They might have been identified by the subjects as general health problems or, in severe instances, identified by physicians as mental disorders. In fact, answers from subjects who received anticholinesterases compared favorably with answers from NCT subjects.

Posttest admissions to Army or VA hospitals for mental disorders did not appear to be significantly increased (Table 18), either during the years immediately after testing or later. The responses to questions about current health status by subjects exposed to anticholinesterases suggest that, as a group, these subjects were no different from the NCT comparison group or from the remainder of the test subjects. If subtle changes occurred, they were not revealed by the subjects' answers about their current health status.

There was a borderline significant increase in malignant neoplasms among soldiers who were admitted to VA hospitals (but not Army hospitals) and were exposed to anticholinesterases, compared with those who received no chemical testing. The neoplasms occurred at various sites, and no consistent pattern was seen. Current animal studies show that this pharmacologic class is unlikely to have induced malignancies among the Edgewood subjects; that conclusion is based on a review of NCI-sponsored lifetime studies of animal bioassay for carcinogenesis at maximal tolerated doses of ten anticholinesterase organophosphate pesticides.[16-25]

ANTICHOLINERGIC CHEMICALS

According to the published literature, the primary health concern for subjects tested with anticholinergics might be short-term cardiovascular effects. No clear indication of such effects over a long period was found. No evidence of differences between these subjects and others was found, with respect to current health status or first admission to a military hospital. All the chemical-test groups showed a trend toward increased rates of admission to Army hospitals per person-year for the first 5 years after testing (Table 12). However, the rate was greatest among the volunteers exposed to anticholinergics. After the first 5 years, there was no evidence of a higher rate among these volunteers than among the others.

An apparent difference in fertility was noted between these subjects and the NCT subjects or OCT subjects (Tables 26 and 27). However, the exposures to anticholinergics occurred relatively late in the series of tests (Table 2). Current age and marital status were taken into account in the estimation of expected values in Tables 26 and 27, but other cohort and social differences might account for the smaller family sizes. There has been a trend toward lower birth rates and greater ages at conception during the last decade.[15] The men exposed to the anticholinergics have the lowest average current age in this population (Table 24), and their lower fertility might reflect these trends in our society. When the appropriate adjustments were performed to take cohort differences into account, the apparent difference between observed and expected fertility rates disappeared (Table 28). It was therefore concluded that there was no evidence of an effect of the anticholinergics on fertility among the exposed men.

There remained, however, a reduction in numbers of male children among the total number of children born after exposure. This reduction was of borderline significance ($p = 0.04$). It was not seen in comparison of males and females among first children born after exposure. Statistics describing proportions of children by sex, such as percentages of male children or sex ratios, are made unreliable by small sample sizes.[12] This small size might have contributed to the finding. No published reports were found of human or animal exposures to anticholinergic chemicals that affected the sex of

offspring. Isolated reports of exposures and later distortions of the proportion of male children have been published in connection with uranium,[8 27] dibromochloropropane (DBCP),[2 11] anesthetic gases,[7] and air pollution containing metals.[4 5] The decrease in the proportion of male children in the present study was judged to be a random finding and was to be expected, because so many comparisons were evaluated.

CHOLINESTERASE REACTIVATORS

A review of the literature disclosed no long-term effects of cholinesterase reactivators (Appendix A). They are eliminated rapidly and produce a variety of short-term, reversible acute effects. These short-term effects might explain in part the slightly increased (nonsignificant) rates of admission to Army hospitals during the first 5 years after testing (Table 12). However, there was no evidence of a difference in current health status between these subjects and the other subjects. Nor was there evidence of differences in the current social functioning of these subjects, e.g., in employment, marital status, and family life.

PSYCHOCHEMICALS

A variety of psychochemicals were tested, including Sernyl (phencyclidine) and dibenzopyrans (dimethylheptylpyran and related compounds). A review of the literature found only sparse evidence of the long-term health effects of these chemicals (Appendix A). The target organs of these substances are the brain and cardiovascular system. However, target mental or cardiovascular effects did not persist beyond a week of exposure to the drugs. It was concluded that, at the dosages used, detectable long-term or delayed effects were unlikely. The data supplied by the soldiers in response to the questionnaire and the patterns of admissions of these soldiers to military hospitals did not contradict these conclusions with regard to specific health effects.

Of particular interest were the 86 soldiers who were exposed to some form of Sernyl, a purified form of phencyclidine. (The impure street form is reported to have undesirable properties; see Vol. 2 of this series.) Of these soldiers, six were known to have died since testing. A total of 48 soldiers returned the questionnaire. The proportion of volunteers ever hospitalized was lowest among those exposed to Sernyl (Table 14). The primary health concern for these subjects was mental disorder. Because few subjects were tested with this compound, the expected number of such admissions was low; in fact, the observed first admissions to Army and VA hospitals for mental disorders were not significantly higher than expected values (Table 18). Similarly, the expected numbers of admissions for malignant neoplasms and diseases of the nervous system were low among this group; no such admissions were observed--an indication that there was

no apparent increase in these health effects among these volunteers. In general, most reported few or no problems and little or no need for health care.

The primary short-term health effects of the dibenzopyrans were moderate to marked and included prolonged orthostatic hypotension. However, there was no indication from the responses on the questionnaire that the current health of exposed subjects was affected.

Of 254 soldiers who were exposed to cannabinoids, 161 returned the questionnaire. This group, as a whole, had the lowest rate of admissions to Army or VA hospitals (Table 15). They did not appear to differ from the other groups in any way assessed by the questionnaire.

IRRITANTS AND VESICANTS

Mustard gas has been shown experimentally to be mutagenic and carcinogenic. Other possible long-term effects, specifically blindness and skin tumors, were expected to be related to local toxicity (Appendix A). However, the soldiers who participated in the Edgewood studies were exposed to mustard gas only at low doses and were wearing gas masks and impregnated clothing. Thirty-eight volunteers had skin damage and erythema after exposure to mustard gas. All these subjects returned the questionnaires; no tumors were associated with skin sites affected as a result of the exposure.

In general, there appeared to be no significant differences in current health status, functioning, or previous hospital admissions between subjects exposed to any of the irritants or vesicants and the rest of the subjects.

LSD DERIVATIVES

Of 571 soldiers exposed to LSD, 317 returned completed questionnaires. This group did not differ from the NCT or OCT subjects in total hospital admissions, admissions for malignant neoplasms or mental disorders, or current health. The soldiers exposed to LSD did, however, have an increased number of first admissions for nervous system and sense organ disorders. There was prestudy concern about a possible increase in suicide rate or epilepsy rate that might result from exposure to LSD. There was no evidence of such effects in the data collected. But the soldiers did report more use of controlled substances. In particular, they reported rates of LSD use higher than expected rates, according to age-specific reported use either by the NCT subjects or by the OCT subjects (Table 30). It is thought that there is underreporting of use of controlled substances, even in self-reporting questionnaires. However, before the testing period, the soldiers were informed as to the substances they might be exposed to; perhaps those who knew that they had been exposed to LSD were more willing to report later use of LSD.

CONCLUSIONS

An 82% response rate was obtained from Edgewood test subjects who were alive, could be located, and received a mailed questionnaire intended to gather information on their current health status.

Long-term health effects of interest were excess cancer and adverse mental, neurologic, hepatic, and reproductive effects that might have resulted from experimental exposure of test subjects to chemicals administered at Edgewood.

A review of the subjects' current use of tobacco, alcoholic beverages, and recreational drugs provided no unusual findings.

Subjects tested with anticholinesterases, anticholinergics, cholinesterase reactivators, or psychochemicals did not differ significantly from NCT or OCT subjects in their replies to questions about current health status. Almost 10% of all respondents reported no health problems related to toxic exposures, and 79% reported good to excellent health. (Subjects tested with LSD were not within the purview of this investigation, inasmuch as they had been evaluated and reported on earlier by a different group, which used other methods. The questionnaire revealed no adverse health effects among these subjects, except for an increase in later use of LSD.)

The subjects tested with irritants and vesicants, including those who received skin burns from mustard gas, reported no significant frequency of adverse health effects or skin cancer.

A review of admissions of Edgewood test subjects to Army hospitals in 1958-1983 and VA hospitals in 1963-1981 and specific admitting diagnoses yielded some interesting findings. Three significant increases were considered possible: (1) malignant neoplasms among men exposed to anticholinesterases and admitted to VA hospitals and (2) nervous system and (3) sense organ disorders among men exposed to LSD and admitted to VA hospitals and to Army hospitals. The numbers of these admissions were small, however, and no evidence of association with exposure to specific chemicals or with dosage was noted.

The experimental methods used in this study and the available comparison groups were such that only large effects were likely to be uncovered. The large standard errors, the initial differences between the exposed and unexposed groups, the possibility that more than one exposure might have led to the same adverse effect, and the self-reporting nature of the questionnaire all would tend to obscure small differences.

TABLE 1

Numbers of Volunteers Tested by Year of Birth
and Year of Beginning of Follow-up

	No. of Men Tested in:[a]				
Year of birth	1955-1959	1960-1964	1965-1969	1970-1975	Total
Before 1920	35	17	--	--	52
1920-1924	55	22	2	--	79
1925-1929	118	78	1	--	197
1930-1934	417	139	17	--	573
1935-1939	491	837	77	17	1,422
1940-1944	47	978	805	69	1,899
1945-1949	--	31	1,191	571	1,793
1950-1954	--	--	18	516	534
After 1954	--	--	1	70	71
Total	1,163	2,102	2,112	1,243	6,620[b]
Mean year of birth:	1934	1939	1945	1950	1942
Mean age at beginning of follow-up year:	23.9	23.5	22.4	22.8	23.1

[a] Follow-up of a volunteer is considered to have begun when his most recent test was completed. (Some subjects had multiple tests.)
[b] Excludes 100 volunteers whose years of birth were missing and who were excluded from mortality analysis.

TABLE 2

Median Years in Which Categories of Chemicals were Administered

Category	Year
Anticholinesterases	1962
Anticholinergics	1968
Cholinesterase reactivators	1968
Sernyl	1959
Irritants	1967
Cannabinoids	1965
LSD derivatives	1959
Approved drugs	1971
Innocuous chemicals and controls	1971

TABLE 3

Probability of Observing Significantly ($p \leq 0.05$, One Tail) Increased Risk Among Exposed Subjects, Compared with NCT Subjects, by True Risk of Outcome in NCT Subjects, Magnitude of Risk Increase Due to Exposure, and Number of Exposed Respondents

No. Exposed Respondents and Magnitude of Risk Increase Due to Exposure	Probability of Detecting Increased Risk if Risk of Outcome Among 1,058 NCT Subjects Is:				
	0.005	0.010	0.050	0.100	0.500
1,000 exposed:					
0.001	0.090	0.077	0.062	0.058	0.055
0.010	0.770	0.545	0.258	0.183	0.117
0.100	1.000	1.000	1.000	1.000	0.998
500 exposed:					
0.001	0.088	0.075	0.060	0.057	0.054
0.010	0.647	0.488	0.211	0.153	0.101
0.100	1.000	1.000	1.000	1.000	0.981
100 exposed:					
0.001	0.080	0.068	0.056	0.054	0.052
0.010	0.395	0.289	0.130	0.100	0.073
0.100	1.000	0.999	0.953	0.870	0.606

TABLE 4

Probability of Observing Significantly ($p \leq 0.05$, One Tail) Increased Risk Among Exposed Subjects, Compared with OCT Subjects, by True Risk of Outcome in OCT Subjects, Magnitude of Risk Increase Due to Exposure, and Number of Exposed and OCT Respondents

No. Exposed Respondents and Magnitude of Risk Increase Due to Exposure	Probability of Detecting Increased Risk if Risk of Outcome Among OCT Subjects Is:				
	0.005	0.010	0.050	0.100	0.500
1,000 exposed (2,027 OCT respondents):					
0.001	0.105	0.086	0.064	0.060	0.056
0.010	0.877	0.718	0.315	0.216	0.130
0.100	1.000	1.000	1.000	1.000	1.000
500 exposed (2,527 OCT respondents):					
0.001	0.100	0.081	0.062	0.058	0.054
0.010	0.748	0.585	0.247	0.173	0.108
0.100	1.000	1.000	1.000	1.000	1.000
100 exposed (2,927 OCT respondents):					
0.001	0.083	0.069	0.056	0.054	0.052
0.010	0.428	0.311	0.135	0.103	0.074
0.100	1.000	0.997	0.957	0.883	0.626

TABLE 5

Attrition of Volunteers Due to Death, Loss to Follow-up, and Failure to Respond to Questionnaire, by Chemical Group (Total)[a]

Chemical Group	Total Tested	Died Before Survey	Alive at Survey No.	Alive at Survey % of Total	Total Located No.	Total Located % of Alive	Respondents No.	Respondents % of Alive	Respondents % of Located
Anticholin-esterases	1,581	87	1,494	94.5	1,179	78.9	995	66.6	84
Anticholinergics	1,805	55	1,750	97.0	1,467	83.8	1,237	70.7	84.3
Cholinesterase reactivators	749	36	713	95.2	596	83.6	495	69.4	83.1
Sernyl	86	6	80	93.0	59	73.8	48	60.0	81.4
Irritants-vesicants	2,135	70	2,065	96.7	1,642	79.5	1,352	65.5	82.3
Cannabinoids	254	6	248	97.6	191	77.0	161	64.9	84.3
LSD	571	30	541	94.7	379	70.1	317	58.6	83.6
None (NCT)	1,894	123	1,771	93.5	1,353	76.4	1,058	59.7	78.2
Total[b]	6,720	325	6,395	95.2	4,996	78.1	4,085	63.9	81.8

[a] Includes total number of volunteers tested with given chemical group, regardless of whether they were tested with chemicals from other chemical groups.

[b] Many volunteers were exposed to chemicals in more than one group.

TABLE 6

Attrition of Volunteers Due to Death, Loss to Follow-up, and Failure to Respond to Questionnaire, by Year of Test Participation

Year of Test Participation	Total Tested	Died Before Survey	Alive at Survey No.	Alive at Survey % of Total	Total Located No.	Total Located % of Alive	Respondents No.	Respondents % of Alive	Respondents % of Located
1955-1959	1,210	118	1,092	90.2	626	57.3	535	49.0	85.5
1960-1964	2,134	116	2,018	94.6	1,635	81.0	1,323	65.6	80.9
1965-1969	2,129	60	2,069	97.2	1,724	83.3	1,399	67.6	81.1
1970-1975	1,247	31	1,216	97.5	1,011	83.1	828	68.1	81.9
Total	6,720	325	6,395	95.2	4,996	78.1	4,085	63.9	81.8

TABLE 7

Number of Requests to Internal Revenue Service for Address Information and Percent of Living Volunteers for Whom "No Record of SSN" was Found, by Chemical Group (Total)[a]

Chemical Group	No. Requests Sent to IRS	"No Record of SSN" No.	"No Record of SSN" %
Anticholinesterases	1,301	37	2.8
Anticholinergics	1,642	36	2.2
Cholinesterase reactivators	661	16	2.4
Sernyl	66	3	4.5
Irritants-vesicants	1,872	53	2.8
Cannabinoids	219	8	3.7
LSD	406	18	4.4
None (NCT)	1,584	54	3.4
Total[b]	5,682	171	3.0

[a] Includes total number of volunteers tested with given chemical group, regardless of whether they were tested with chemicals from other chemical groups.

[b] Many volunteers were exposed to chemicals in more than one group.

TABLE 8

Rate of Response to Questionnaire

Response	Living Volunteers No.	Living Volunteers % of Alive	Living Volunteers % of Located
Total located	4,996	78.1	100.0
Completed	4,085	63.9	81.8
Refused	100	1.6	2.0
No response	811	12.7	16.2
Wrong address	624	9.8	--
No address	775	12.1	--
Total	6,395	100.0	100.0

TABLE 9

Volunteers Who Were Exposed to Anticholinesterases and Requested Results of Study[a]

(A Sample of the Computer Tables Used in the Preliminary Screening of Data)

Age in 1984, Years	Requested		Volunteers Exposed to Anticholinesterases: A ALN	A AND	TTL A	CNTRL	OTHER	NOT A	TOTAL
Under 35	Yes	No.	1	27	28	104	211	315	343
		%	100.0	96.4	96.6	86.7	92.1	90.3	90.7
	No	No.	0	1	1	16	18	34	35
		%	--	3.6	3.4	13.3	7.9	9.7	9.3
	Total	No.	1	28	29	120	229	349	378
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
35-39	Yes	No.	6	80	86	234	699	933	1,019
		%	85.7	84.2	84.3	82.4	85.0	84.4	84.4
	No	No.	1	15	16	50	123	173	189
		%	14.3	15.8	15.7	17.6	15.0	15.6	15.6
	Total	No.	7	95	102	284	822	1,106	1,208
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
40-44	Yes	No.	96	275	371	227	438	665	1,036
		%	82.1	87.0	85.7	77.7	84.9	82.3	83.5
	No	No.	21	41	62	65	78	143	205
		%	17.9	13.0	14.3	22.3	15.1	17.7	16.5
	Total	No.	117	316	433	292	516	808	1,241
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
45-49	Yes	No.	79	169	248	187	239	426	674
		%	81.4	86.7	84.9	80.6	85.1	83.0	83.7
	No	No.	18	26	44	45	42	87	131
		%	18.6	13.3	15.1	19.4	14.9	17.0	16.3
	Total	No.	97	195	292	232	281	513	805
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
50-54	Yes	No.	37	31	68	49	106	155	223
		%	92.5	83.8	88.3	63.6	84.1	76.4	79.6
	No	No.	3	6	9	28	20	48	57
		%	7.5	16.2	11.7	36.4	15.9	23.6	20.4
	Total	No.	40	37	77	77	126	203	280
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0

TABLE 9 (continued)

Age in 1984, Years	Requested		A ALN	A AND	TTL A	CNTRL	OTHER	NOT A	TOTAL
55 and over	Yes	No.	19	26	45	41	45	86	131
		%	67.9	76.5	72.6	77.4	77.6	77.5	75.7
	No	No.	9	8	17	12	13	25	42
		%	32.1	23.5	27.4	22.6	22.4	22.5	24.3
		No.	28	34	62	53	58	111	173
	Total	%	100.0	100.0	100.0	100.0	100.0	100.0	100.0
TOTAL	Yes	No.	238	608	846	842	1,738	2,580	3,426
		%	82.1	86.2	85.0	79.6	85.5	83.5	83.9
	No	No.	52	97	149	216	294	510	659
		%	17.9	13.8	15.0	20.4	14.5	16.5	16.1
	Total	No.	290	705	995	1,058	2,032	3,090	4,085
		%	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[a] A ALN (Alone): Persons who participated in tests of the category of chemical named in the table heading and no others (in this example, the anticholinesterases).
A AND: Persons who participated in tests of the category named and in tests of at least one other category.
TTL A: The sum of A ALN and A AND (i.e., all persons exposed to the category named).
CNTRL: The no-chemical-test (NCT) comparison group defined earlier.
OTHER: All subjects in chemical tests except those involving the category named, i.e., the other-chemical-test (OCT) comparison group.
NOT A: All subjects (including the NCT group) minus volunteers who participated in tests involving the named category (i.e., the sum of CNTRL and OTHER).
TOTAL: All respondents (i.e., the sum of TTL A and NOT A).

TABLE 10

Outcome Characteristics Evaluated in This Report

Posttest Army hospital admission
- First admissions for:[a]
  - Malignant neoplasms (ICD-8, codes 140-239)
  - Mental disorders (ICD-8, codes 290-315)
  - Diseases of nervous system and sense organs (ICD-8, codes 320-389)

Postseparation VA hospital admission
- First admissions for:[a]
  - Malignant neoplasms (ICD-8, codes 140-239)
  - Mental disorders (ICD-8, codes 290-315)
  - Diseases of nervous system and sense organs (ICD-8, codes 320-389)

Questionnaire responses:
- Self-rating of health
- Marital history:
  - Current marital status
  - Times married
- Present living arrangements
- Employment history:
  - Number of jobs reported
  - Current occupation
- Liveborn children:
  - Number of children
  - Sex of children
  - Birth defects
  - Current survival status of children
- Health problems due to toxic exposure
- Smoking history:
  - Ever smoked
  - Current smoking
- Use of alcoholic beverages:
  - Daily use
  - History of abuse
- Use of controlled substances
- Medical problems:
  - Illness, preceding 5 years
  - Hospitalized, preceding 5 years
  - Confined to bed, preceding month
- Impairments:
  - Work, chores
  - Personal care

[a] ICD-8 = Eighth Revision International Classification of Diseases.

TABLE 11

Admissions to Army Hospitals and Admission Rates
Per 1,000 Person-Years of Observation, by Years Since Testing
(Volunteers Exposed to Only One Chemical Group)

Chemical Group	Years Since Testing 0-4	5-9	10-14	15-19	20+	Total
			No. Admissions			
Anticholinesterases	46	31	36	37	21	171
Anticholinergics	76	29	37	9	4	155
Cholinesterase reactivators	19	2	2	--	--	23
Sernyl	2	--	3	--	--	5
Irritants-vesicants	116	66	51	22	10	265
Cannabinoids	9	--	1	--	3	13
LSD	18	14	21	29	15	97
None (NCT)	398	137	129	81	31	776
			No. Person-Years of Observation			
Anticholinesterases	1,878.0	1,791.0	1,709.5	1,560.0	1,110.5	8,049.0
Anticholinergics	1,767.0	1,442.0	1,298.0	791.5	226.0	5,524.5
Cholinesterase reactivators	292.0	237.0	230.0	131.0	85.0	975.0
Sernyl	105.5	96.0	93.0	90.0	88.0	472.5
Irritants-vesicants	2,876.0	2,511.0	2,363.0	1,247.0	737.0	9,734.0
Cannabinoids	133.5	121.0	114.0	85.0	26.0	479.5
LSD	1,034.0	981.0	911.0	802.0	921.0	4,649.0
None (NCT)	6,407.0	5,393.5	4,856.0	3,671.0	1,885.0	22,212.5
			Admission Rates Per 1,000 Person-Years			
Anticholinesterases	24.5	17.3	21.1	23.7	18.9	21.2
Anticholinergics	43.0	20.1	28.5	11.4	17.7	28.1
Cholinesterase reactivators	65.1	8.4	8.7	--	--	23.6
Sernyl	19.0	--	32.3	--	--	10.6
Irritants-vesicants	40.3	26.3	21.6	17.6	13.6	27.2
Cannabinoids	67.4	--	8.8	--	115.4	27.1
LSD	17.4	14.3	23.1	36.2	16.3	20.9
None (NCT)	62.1	25.4	26.6	22.1	16.4	34.9

TABLE 12

Admissions to Army Hospitals and Admission Rates
Per 1,000 Person-Years of Observation, by Years Since Testing
(Volunteers Exposed to More than One Chemical Group)

Chemical Group	Years Since Testing 0-4	5-9	10-14	15-19	20+	Total
			No. Admissions			
Anticholinesterases	109	58	64	45	14	290
Anticholinergics	187	67	55	24	2	335
Cholinesterase reactivators	90	54	31	25	7	207
Sernyl	10	1	2	4	1	18
Irritants-vesicants	152	75	51	31	9	318
Cannabinoids	21	14	7	8	1	51
LSD	38	19	27	12	5	101
None (NCT)	398	137	129	81	31	776
			No. Person-Years of Observation			
Anticholinesterases	3,936.5	3,600.5	3,415.5	2,813.0	1,354.5	15,125.0
Anticholinergics	4,180.5	3,620.0	3,347.5	2,007.0	407.0	13,562.0
Cholinesterase reactivators	2,181.0	1,853.0	1,703.0	1,248.0	463.0	7,448.0
Sernyl	262.0	241.5	211.5	221.0	204.0	1,140.0
Irritants-vesicants	4,312.0	3,904.5	3,647.0	2,180.0	997.0	15,040.5
Cannabinoids	850.0	758.5	745.0	527.0	149.5	3,030.0
LSD	1,195.0	1,105.0	1,061.0	900.0	573.5	4,834.5
None (NCT)	6,407.0	5,393.5	4,856.0	3,671.0	1,885.0	22,212.5
			Admission Rates Per 1,000 Person-Years			
Anticholinesterases	27.7	16.1	18.7	16.0	10.3	19.2
Anticholinergics	44.7	18.5	16.4	12.0	4.9	24.7
Cholinesterase reactivators	41.3	29.1	18.2	20.0	15.1	27.8
Sernyl	38.2	4.1	9.5	18.1	4.9	15.8
Irritants-vesicants	35.3	19.2	14.0	14.2	9.0	21.1
Cannabinoids	24.7	18.5	9.4	15.2	6.7	16.8
LSD	31.8	17.2	25.4	13.3	8.7	20.9
None (NCT)	62.1	25.4	26.6	22.1	16.4	34.9

TABLE 13

Volunteers Admitted to Army Hospitals and Percent of Volunteers Still in Service Who Were Hospitalized, by Years Since Testing (Volunteers Exposed to Only One Chemical Group)

Chemical Group	Years Since Testing 0-4	5-9	10-14	15-19	20-24	25+
	No. Volunteers with Any Admissions					
Anticholinesterases	32	22	20	21	10	1
Anticholinergics	58	18	19	7	3	--
Cholinesterase reactivators	13	2	2	--	--	--
Sernyl	2	--	2	--	--	--
Irritants-vesicants	75	28	27	12	7	--
Cannabinoids	4	--	1	--	3	--
LSD	17	9	11	13	8	1
None (NCT)	251	85	68	43	13	1
	No. Volunteers Still in Service (Mean)					
Anticholinesterases	376	358	342	312	184	50
Anticholinergics	353	288	260	158	44	2
Cholinesterase reactivators	58	47	46	26	16	8
Sernyl	21	19	19	18	17	4
Irritants-vesicants	575	502	473	249	120	34
Cannabinoids	27	24	23	17	5	4
LSD	207	196	182	160	145	72
None (NCT)	1,281	1,079	971	734	333	44
	Percent of Volunteers Hospitalized					
Anticholinesterases	8.5	6.1	5.8	6.7	5.4	2.0
Anticholinergics	16.4	6.3	7.3	4.4	6.8	--
Cholinesterase reactivators	22.4	4.3	4.3	--	--	--
Sernyl	9.5	--	10.5	--	--	--
Irritants-vesicants	13.0	5.6	5.7	4.8	5.8	--
Cannabinoids	14.8	--	4.3	--	60.0	--
LSD	8.2	4.6	6.0	8.1	5.5	1.4
None (NCT)	19.6	7.9	7.0	5.9	3.9	2.3

TABLE 14

Volunteers Admitted to Army Hospitals and Percent of Volunteers Still in Service Who Were Hospitalized, by Years Since Testing (Volunteers Exposed to More than One Chemical Group)

Chemical Group	Years Since Testing 0-4	5-9	10-14	15-19	20-24	25+
	No. Volunteers with Any Admissions					
Anticholinesterases	79	38	36	24	8	1
Anticholinergics	121	45	37	11	2	--
Cholinesterase reactivators	67	29	20	11	3	--
Sernyl	5	1	2	3	1	--
Irritants-vesicants	100	48	34	17	6	2
Cannabinoids	11	7	4	3	1	--
LSD	23	13	19	10	5	--
None (NCT)	251	85	68	43	13	1
	No. Volunteers Still in Service (Mean)					
Anticholinesterases	787	720	683	564	240	39
Anticholinergics	836	724	670	401	73	10
Cholinesterase reactivators	436	371	341	250	92	3
Sernyl	52	48	45	44	40	4
Irritants-vesicants	862	781	729	436	160	50
Cannabinoids	170	152	149	105	27	9
LSD	239	221	212	180	104	20
None (NCT)	1,281	1,079	971	734	333	44
	Percent of Volunteers Hospitalized					
Anticholinesterases	10.0	5.3	5.3	4.3	3.3	2.6
Anticholinergics	14.5	6.2	5.5	2.7	2.7	--
Cholinesterase reactivators	15.4	7.8	5.9	4.4	3.3	--
Sernyl	9.6	2.1	4.4	6.8	2.5	--
Irritants-vesicants	11.6	6.1	4.7	3.9	3.8	4.0
Cannabinoids	6.5	4.6	2.7	2.9	3.7	--
LSD	9.6	5.9	9.0	5.6	4.8	--
None (NCT)	19.6	7.9	7.0	5.9	3.9	2.3

TABLE 15

Admissions to VA Hospitals and Admission Rates Per 1,000 Person-Years of Observation, by Years Since Separation from Service (Volunteers Exposed to Only One Chemical Group)

Chemical Group	Years Since Separation 0-4	5-9	10-14	15-19	20-29	Total
			No. Admissions			
Anticholinesterases	13	8	13	17	8	59
Anticholinergics	43	14	11	1	--	69
Cholinesterase reactivators	--	--	--	--	--	--
Sernyl	--	--	1	--	--	1
Irritants-vesicants	40	39	32	12	3	126
Cannabinoids	3	1	--	--	--	4
LSD	2	16	9	12	10	49
None (NCT)	114	126	140	123	48	551
			No. Person-Years of Observation			
Anticholinesterases	1,319.5	1,473.5	1,366.0	1,153.0	482.5	5,894.5
Anticholinergics	1,927.0	1,834.5	1,358.5	622.5	150.5	5,893.0
Cholinesterase reactivators	313.0	323.5	253.0	101.5	42.5	1,033.5
Sernyl	51.0	75.0	72.0	66.0	48.0	312.0
Irritants-vesicants	3,047.5	3,071.0	2,517.0	809.0	283.0	9,727.5
Cannabinoids	103.0	102.0	90.5	57.0	5.0	357.5
LSD	501.0	707.0	603.0	467.0	409.0	2,687.0
None (NCT)	5,838.0	5,881.5	4,606.0	2,628.0	1,117.0	20,070.5
			Admission Rates Per 1,000 Person-Years			
Anticholinesterases	9.9	5.4	9.5	14.7	16.6	10.0
Anticholinergics	22.3	7.6	8.1	1.6	--	11.7
Cholinesterase reactivators	--	--	--	--	--	--
Sernyl	--	--	13.9	--	--	3.2
Irritants-vesicants	13.1	12.7	12.7	14.8	10.6	13.0
Cannabinoids	29.1	9.8	--	--	--	11.2
LSD	4.0	22.6	19.9	25.7	24.4	18.2
None (NCT)	19.5	21.4	30.4	46.8	43.0	27.5

TABLE 16

Admissions to VA Hospitals and Admission Rates Per 1,000 Person-Years of Observation, by Years Since Separation from Service (Volunteers Exposed to More Than One Chemical Group)

Chemical Group	Years Since Separation 0-4	5-9	10-14	15-19	20+	Total
			No. Admissions			
Anticholinesterases	37	31	36	22	7	133
Anticholinergics	55	40	28	6	5	134
Cholinesterase reactivators	12	17	16	13	6	64
Sernyl	2	15	15	5	1	38
Irritants-vesicants	64	59	27	19	18	187
Cannabinoids	2	6	6	1	--	15
LSD	14	14	12	6	15	61
None (NCT)	114	126	140	123	48	551
			No. Person-Years of Observation			
Anticholinesterases	3,457.0	3,577.5	3,243.0	2,347.5	1,261.0	13,886.0
Anticholinergics	4,548.5	4,369.0	3,473.0	1,596.0	245.0	14,231.5
Cholinesterase reactivators	2,288.0	2,211.5	1,720.5	1,086.0	290.0	7,596.0
Sernyl	119.0	162.0	159.0	133.0	94.0	667.0
Irritants-vesicants	4,137.0	4,147.0	3,316.0	1,531.0	490.5	13,621.5
Cannabinoids	739.0	749.0	713.5	384.5	42.5	2,628.5
LSD	869.0	974.0	880.5	702.0	282.0	3,707.5
None (NCT)	5,838.0	5,881.5	4,606.0	2,628.0	1,117.0	20,070.5
			Admission Rates Per 1,000 Person-Years			
Anticholinesterases	10.7	8.7	11.1	9.4	5.6	9.6
Anticholinergics	12.1	9.2	8.1	3.8	20.4	9.4
Cholinesterase reactivators	5.2	7.7	9.3	12.0	20.7	8.4
Sernyl	16.8	92.6	94.3	37.6	10.6	57.0
Irritants-vesicants	15.5	14.2	8.1	12.4	36.7	13.7
Cannabinoids	2.7	8.0	8.4	2.6	--	5.7
LSD	16.1	14.4	13.6	8.5	53.2	16.5
None (NCT)	19.5	21.4	30.4	46.8	43.0	27.5

TABLE 17

Observed and Expected First Admissions for Malignant Neoplasms at Army and VA Hospitals After Time of Testing (ICD-8, Codes 140-209) (All Volunteers)

Chemical Group	No. First Admissions to Army Hospitals			No. First Admissions to VA Hospitals		
	OCT Exp.[a]	Obs.	NCT Exp.[b]	OCT Exp.[a]	Obs.	NCT Exp.[b]
Anticholinesterases	1.0	2	2.5	1.0	4	0.0
Other chemical tests	--	2	5.1	--	2	0.0
Anticholinergics	2.4	0	2.9	1.8	3	0.0
Other chemical tests	--	4	4.8	--	3	0.0
Cholinesterase reactivators	0.7	0	1.2	0.7	2	0.0
Other chemical tests	--	4	6.5	--	4	0.0
Sernyl	0.1	0	0.1	0.1	0	0.0
Other chemical tests	--	4	7.5	--	6	0.0
Irritants-vesicants	1.6	2	3.4	3.2	2	0.0
Other chemical tests	--	2	4.3	--	4	0.0
Cannabinoids	0.2	0	0.4	0.3	0	0.0
Other chemical tests	--	4	7.2	--	6	0.0
LSD	0.4	1	0.9	0.7	1	0.0
Other chemical tests	--	3	6.7	--	5	0.0
None (NCT)	--	3	3.0	--	0	0.0
Total volunteers	--	7	10.6	--	6	0.0

[a] Based on all other chemical tests: number of volunteers tested with this chemical group times proportion of volunteers with first admissions among those tested with any group except this one (OCT).

[b] Based on no-chemical-test group experience: number of volunteers tested with this chemical group times proportion of volunteers with first admissions among those not tested with any chemical group (NCT).

TABLE 18

Observed and Expected First Admissions for Mental Disorders at Army and VA Hospitals After Time of Testing (ICD-8, Codes 290-315) (All Volunteers)

Chemical Group	No. First Admissions to Army Hospitals			No. First Admissions to VA Hospitals		
	OCT Exp.[a]	Obs.	NCT Exp.[b]	OCT Exp.[a]	Obs.	NCT Exp.[b]
Anticholinesterases	9.7	14	18.4	24.4	20	32.6
Other chemical tests	--	20	37.7	--	50	66.8
Anticholinergics	11.4	15	21.0	29.3	21	37.2
Other chemical tests	--	19	35.1	--	49	62.2
Cholinesterase reactivators	5.0	7	8.7	11.0	10	15.4
Other chemical tests	--	27	47.4	--	60	84.0
Sernyl	0.6	2	1.0	1.2	2	1.8
Other chemical tests	--	32	55.1	--	68	97.6
Irritants-vesicants	18.2	11	24.8	31.7	30	44.0
Other chemical tests	--	23	31.3	--	40	55.4
Cannabinoids	1.9	0	3.0	3.8	2	5.2
Other chemical tests	--	34	53.1	--	68	94.1
LSD	4.0	4	6.6	8.5	7	11.8
Other chemical tests	--	30	49.4	--	63	87.6
None (NCT)	--	22	22.0	--	39	39.0
Total volunteers	--	56	78.1	--	109	138.4

[a] Based on all other chemical tests: number of volunteers tested with this chemical group times proportion of volunteers with first admissions among those tested with any group except this one (OCT).

[b] Based on no-chemical-test group experience: number of volunteers tested with this chemical group times proportion of volunteers with first admissions among those not tested with any chemical group (NCT).

TABLE 19

Observed and Expected First Admissions for Diseases of Nervous System and Sense Organs at Army and VA Hospitals After Time of Testing (ICD-8, Codes 320-389) (All Volunteers)

Chemical Group	No. First Admissions to Army Hospitals			No. First Admissions to VA Hospitals		
	OCT Exp.[a]	Obs.	NCT Exp.[b]	OCT Exp.[a]	Obs.	NCT Exp.[b]
Anticholinesterases	11.7	11	6.7	4.9	3	2.5
Other chemical tests	--	24	13.7	--	10	5.1
Anticholinergics	16.7	7	7.6	3.6	7	2.9
Other chemical tests	--	28	12.8	--	6	4.8
Cholinesterase reactivators	5.5	5	3.2	1.8	3	1.2
Other chemical tests	--	30	17.2	--	10	6.5
Sernyl	0.6	0	0.4	0.2	0	0.1
Other chemical tests	--	35	20.0	--	13	7.5
Irritants-vesicants	19.0	11	9.0	7.1	4	3.4
Other chemical tests	--	24	11.4	--	9	4.3
Cannabinoids	1.8	2	1.1	0.7	1	0.4
Other chemical tests	--	33	19.3	--	12	7.2
LSD	3.8	7	2.4	1.2	4	0.9
Other chemical tests	--	28	18.0	--	9	6.7
None (NCT)	--	8	8.0	--	3	3.0
Total volunteers	--	43	28.4	--	16	10.6

[a] Based on all other chemical tests: number of volunteers tested with this chemical group times proportion of volunteers with first admissions among those tested with any group except this one (OCT).

[b] Based on no-chemical-test group experience: number of volunteers tested with this chemical group times proportion of volunteers with first admissions among those not tested with any chemical group (NCT).

TABLE 20

Numbers and Percent of Living Volunteers Still in Service Admitted to Army Hospitals, by Years Since Testing and Response

No. Years Since Testing	Responded to Questionnaire: Yes	Responded to Questionnaire: No[a]	Unable to locate[b]: No.	Unable to locate[b]: % of Living
	No. Still in Service (Mean)[c]			
0-4	2,811	642	1,122	24.5
5-9	2,436	549	1,021	25.5
10-14	2,241	511	953	25.7
15-19	1,512	350	822	30.6
20-24	598	128	520	41.7
	No. Hospitalized			
0-4	388	90	186	28.0
5-9	184	28	46	17.8
10-14	157	30	34	15.4
15-19	91	19	21	16.0
20-24	45	6	6	10.5
	% Hospitalized Among Those in Service			
0-4	13.8	14.0	16.6	--
5-9	7.6	5.1	4.5	--
10-14	7.0	5.9	3.6	--
15-19	6.0	5.4	2.6	--
20-24	7.5	4.7	1.2	--

[a] Includes refusals and mailings without Post Office notification of incorrect address.

[b] Includes mailings returned by Post Office with notification of incorrect address.

[c] Number of men still in service was counted for each year after testing; mean annual number of men estimated for each 5-year posttest interval.

TABLE 21

Results of Attempt to Interview Nonrespondents,
by Chemical Group (Total)

Chemical Group	No. Non-respondents	Results of attempt to interview nonrespondents: Interviewed No.	Interviewed %	Refused No.	Refused %	No contact[a] No.	No contact[a] %
Anticholinesterases	183	135	73.8	5	2.7	43	23.5
Anticholinergics	224	167	74.6	9	4.0	48	21.4
Cholinesterase reactivators	105	80	76.2	4	3.8	21	20.0
Sernyl	11	10	90.9	0	--	1	9.1
Irritants-vesicants	286	203	71.0	15	5.2	68	23.8
Cannabinoids	32	24	75.0	2	6.3	6	18.8
LSD	58	43	74.1	4	6.9	11	19.0
None (NCT)	283	212	74.9	7	2.5	64	22.6
Total[b]	891	657	73.7	36	4.0	198	22.2

[a] Reasons for no contact:

Language barrier	1
Deceased	17
Out of country	23
Unable to contact	83
Unable to locate	74

[b] Many volunteers were exposed to chemicals in more than one group.

TABLE 22

Response to Receipt of Questionnaire by 643 Interviewed Men Who Were on Special Assignment to Aberdeen Proving Ground, by Chemical Group (Total)

Chemical Group	No. Interviewed	Received Questionnaire	
		No.	%
Anticholinesterases	135	117	86.7
Anticholinergics	162	134	82.7
Cholinesterase reactivators	80	67	83.8
Sernyl	9	5	55.6
Irritants-vesicants	197	172	87.3
Cannabinoids	23	22	95.7
LSD	43	35	81.4
None (NCT)	208	164	78.8
Total[a]	643[b]	541	84.1

[a] Many volunteers were exposed to chemicals in more than one group.

[b] Excludes 14 respondents who were never on special assignment to Aberdeen Proving Ground.

TABLE 23

Reasons Given for Not Replying to Questionnaire by Deadline by 541 Interviewed Men Who Were on Special Assignment to Aberdeen Proving Ground, by Chemical Group (Total)

Chemical Group	No. Who Received Questionnaire	Claimed to Have Responded[b]		Reasons for Not Responding[a]					
				No Health Problems to Report		Too Personal		Concerned About Confidentiality	
		No.	%	No.	%	No.	%	No.	%
Anticholinesterases	117	17	14.5	72	61.5	22	18.8	25	21.4
Anticholinergics	134	14	10.4	86	64.2	31	23.1	37	27.6
Cholinesterase reactivators	67	11	16.4	39	58.2	15	22.4	17	25.4
Sernyl	5	1	20.0	4	80.0	2	40.0	1	20.0
Irritants-vesicants	172	19	11.0	110	64.0	44	25.6	43	25.0
Cannabinoids	22	4	18.2	14	63.6	2	9.1	6	27.3
LSD	35	4	11.4	20	57.1	9	25.7	11	31.4
None (NCT)	164	17	10.4	103	62.8	29	17.7	45	27.4
Total[c]	541	62	11.5	337	62.3	114	21.1	135	25.0

[a] Many checked more than one reason for not responding.
[b] Thirteen of these claimed responses were eventually received, including seven received too late to be included in analysis.
[c] Many volunteers were exposed to chemicals in more than one group.

TABLE 24

Age of Respondents, by Chemical Group
(All Volunteers Who Responded)

Age in 1984, years	Chemical Group: Anticholinesterases	Anticholinergics	Cholinesterase Reactivators	Sernyl	Irritants-Vesicants	Cannabinoids	LSD	None (NCT)	Total[a]
				No. Respondents					
Under 35	29	174	75	0	98	0	0	120	378
35-39	102	437	113	0	601	45	24	284	1,208
40-44	433	427	184	5	384	86	77	292	1,241
45-49	292	153	96	30	171	20	118	232	805
50-54	77	31	15	6	69	7	62	77	280
55+	62	15	12	7	29	3	36	53	173
Total	995	1,237	495	48	1,352	161	317	1,058	4,085
Mean age, years	44.9	40.4	41.5	49.1	41.0	42.4	47.6	42.6	42.4
				% of Respondents					
Under 35	2.9	14.1	15.2	--	7.2	--	--	11.3	9.3
35-39	10.3	35.3	22.8	--	44.5	28.0	7.6	26.8	29.6
40-44	43.5	34.5	37.2	10.4	28.4	53.4	24.3	27.6	30.4
45-49	29.3	12.4	19.4	62.5	12.6	12.4	37.2	21.9	19.7
50-54	7.7	2.5	3.0	12.5	5.1	4.3	19.6	7.3	6.9
55+	6.2	1.2	2.4	14.6	2.1	1.9	11.4	5.0	4.2
Total	99.9	100.0	100.0	100.0	99.9	100.0	100.1	99.9	100.1

[a] Many volunteers were exposed to chemicals in more than one group.

TABLE 25

Education of Respondents, by Chemical Group
(All Volunteers Who Responded)

Education Completed, years	Chemical Group: Anticholinesterases	Anticholinergics	Cholinesterase Reactivators	Sernyl	Irritants-Vesicants	Cannabinoids	LSD	None (NCT)	Total[a]
				No. Respondents					
Less than 6	0	1	1	0	0	0	0	1	2
6-8	12	4	2	0	8	1	9	13	38
9-11	41	35	25	5	55	4	13	52	175
12	441	478	197	26	565	75	140	435	1,697
13-16	380	561	211	10	571	62	112	419	1,662
17 or more	92	141	53	7	120	14	40	103	412
Not reported	29	17	6	0	33	5	3	35	99
Total	995	1,237	495	48	1,352	161	317	1,058	4,085
				% of Respondents					
Less than 6	--	0.1	0.2	--	--	--	--	0.1	0.05
6-8	1.2	0.3	0.4	--	0.6	0.6	2.8	1.2	0.9
9-11	4.1	2.8	5.1	10.4	4.1	2.5	4.1	4.9	4.3
12	44.3	38.6	39.8	54.2	41.8	46.6	44.2	41.1	41.5
13-16	38.2	45.4	42.6	20.8	42.2	38.5	35.3	39.6	40.7
17 or more	9.2	11.4	10.7	14.6	8.9	8.7	12.6	9.7	10.1
Not reported	2.9	1.4	1.2	--	2.4	3.1	0.9	3.3	2.4
Total	99.9	100.0	100.0	100.0	100.0	100.0	99.9	99.9	99.9
Median, years	13.0	13.7	13.4	12.7	13.3	13.0	13.0	13.3	13.3

[a] Many volunteers were exposed to chemicals in more than one group.

Table 26

Observed and Expected Numbers of Men Exposed to Anticholinergics, with Adjustment for Age of Comparison Groups, by Total Numbers of Reported Children (Includes Sex Not Reported)

No. Liveborn Offspring	No. Subjects: Anticholinergics Alone Obs.	Alone NCT Exp.[a]	Anticholinergics Plus Others Obs.	Plus Others NCT Exp.[a]	Anticholinergics, Total Obs.	Total OCT Exp.[b]
0	99	74.6	221	184.0	320	254.6
1	51	66.6	151	165.2	202	232.5
2	117	111.3	312	283.0	429	426.5
3-5	83	94.9	191	237.8	274	311.4
6-9	3	5.7	9	14.0	12	12.0
Total	353	353.1	884	884.0	1,237	1,237.0
Mean	1.81	2.01	1.81	2.01	1.81	1.95

Chi-square test summary:

X_1^{2c}	5.97	4.85	12.22
p	$0.05 > p > 0.01$	$0.05 > p > 0.01$	$0.001 > p$

[a] Expected numbers derived from age-specific reproduction history of NCT subjects.

[b] Expected numbers derived from age-specific reproduction history of OCT subjects.

[c] Mantel-Haenszel test of no children vs. one or more children with stratification on age in 1984.

TABLE 27

Observed and Expected Numbers of Men Exposed to Anticholinergics (Total), with Adjustment for Age and Marital Status of OCT Group, by Total Numbers of Reported Children (Includes Sex Not Reported)

No. Liveborn Offspring	No. Subjects Observed	Expected	Ratio of Reported to Expected
0	320	246.3	1.30
1	202	211.9	0.95
2	429	406.4	1.06
3-5	274	349.9	0.78
6-9	12	22.6	0.53
Total	1,237		
Mean	1.81	2.09	

$X_1^2 = 13.20^a$ $p < 0.001$

[a] Mantel-Haenszel test of no children vs. one or more children with stratification on marital status and age in 1984.

TABLE 28

Numbers and Sex of Offspring of Men Exposed to Anticholinergics (Total), by Year Since Testing, and Expected Values, Adjusted for Age and Year of Testing with OCT Group as Reference

Time of Birth	No. Males		No. Females		Total[a]	
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
Before testing to 1 year after testing	138	139.3	140	133.3	282	276.7
2-4 years after testing	198	215.0	215	198.7	416	415.7
5-7 years after testing	223	237.9	276	265.8	509	505.9
8-10 years after testing	192	228.2	199	191.5	402	426.2
11+ years after testing	208	219.3	199	214.6	418	443.5
2 or more years after testing	821	900.4	889	870.6	1,745	1,791.3
X^2 test summary[b]						
X^2	4.32		0.0005		0.935	
p	$0.05 > p > 0.01$		$p > 0.1$		$p > 0.1$	

[a] Includes children of unknown sex.
[b] Mantel-Haenszel test with stratification on age (5-year groups) and calendar year of testing (1955-1961, 1962-1968, 1969-1975).

TABLE 29

Reported Use of Substances of Abuse Among All 4,C85 Respondents

Substance	Never Used		Used 1-9 Times		Used 10 or More Times		Not Stated	
	No.	%	No.	%	No.	%	No.	%
Amphetamines, other stimulants	3,073	75.2	386	9.4	340	8.3	286	7.0
Barbiturates, other depressants	3,327	81.4	267	6.5	160	3.9	331	8.1
Cocaine	3,378	82.7	232	5.7	168	4.1	307	7.5
Heroin	3,661	89.6	47	1.2	45	1.1	332	8.1
LSD	3,299	80.8	372	9.1	106	2.6	308	7.5
Marijuana	2,351	57.6	743	18.2	763	18.7	228	5.6
Phencyclidine	3,629	88.8	88	2.2	24	0.6	344	8.4
Other narcotics, opiates	2,432	59.5	956	23.4	433	10.6	264	6.5
Tranquilizers	2,665	65.2	699	17.1	471	11.5	250	6.1

TABLE 30

Reported and Age-Adjusted Expected Use of LSD by Volunteers Tested with LSD

Reported Times LSD Used	No. Subjects in Test Category: LSD Alone Obs.	LSD Alone Exp.[a]	LSD and Other Chemicals Obs.	LSD and Other Chemicals Exp.[a]	Total LSD Obs.	Total LSD Exp.[b]
0	36	85.9	103	195.0	139	278.4
1-9	49	1.6	92	4.5	141	10.2
Less than 10 (sum)	85	87.5	195	199.5	280	288.6
10-99	4	0.2	4	1.0	8	2.2
100-999	0	0.0	0	0.0	0	0.0
1,000 or more	0	0.0	1	0.0	1	0.0
10 or more (sum)	4	0.2	5	1.0	9	2.2
Unknown	9	10.3	19	18.5	28	26.2
Total	98	98.0	219	219.0	317	317.0

Mantel-Haenszel X^2 test summary:[c]

X^2	6.10	4.07	5.97
p	$0.02 > p > 0.01$	$0.05 > p > 0.02$	$0.02 > p > 0.01$

[a] Derived from age-specific reported use of LSD by subjects exposed to no chemicals.

[b] Derived from age-specific reported use of LSD by subjects exposed to chemicals except LSD.

[c] Reported use: less than 10 times vs. 10 or more times (excluding use not reported).

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APPENDIX A

EXECUTIVE SUMMARIES OF VOLUMES 1 AND 2

EXECUTIVE SUMMARY OF VOLUME 1

In response to a request from the Department of the Army, the Committee on Toxicology (COT) of the National Research Council Assembly of Life Sciences conducted a study to evaluate the possibility of long-term or delayed adverse health effects of chemical agents tested on military volunteers during the 1960s and 1970s.

The task was begun about 2 years ago, with interviews of key people who had been associated with the soldier-volunteer test program of the Army Chemical Center (Edgewood Arsenal), Maryland. Initial efforts included a thorough review of the Army's laboratory and clinical records and of reports in the scientific literature. Some 6,720 soldiers took part in the Edgewood program as test subjects in about 1958-1975, and 24 chemicals were administered in an experimental setting.

The chemicals were divided into eight major pharmacologic classes and organized within each class according to structure. The most extensively studied classes are the anticholinergic and the anticholinesterase chemicals, and these are the subjects of this report; the other classes will be reported on later. Panels were then formed to study these two main classes. The chairmen were selected for expertise in some aspect of the review of the pharmacologic class in question.

The anticholinesterases are generally organophosphates; these are nerve agents resembling parathion. Major symptoms of low-level anticholinesterase exposure include salivation, increased sweating, contracted pupils, and bronchospasm. The anticholinergics are generally "glycolates," (substituted glycolic and tropic acid esters) of which the representative and best-known member is atropine. Major symptoms of low-level atropinization include dry mouth, dilated pupils, and tachycardia. There were 24 anticholinergics tested on about 1,800 subjects. There were 15 anticholinesterases tested on about 1,400 subjects. These two classes are readily paired, in that members of each are used as treatment for overexposure to members of the other.

The next step involved organization of Edgewood data and reports. Some of this material had to be declassified before use by the panels. Digests of the entire available literature, classified and

unclassified, were prepared by consultant pharmacologists, and various documents were made available to the panels for use in investigating the possibility that the Edgewood test experience resulted in persistent adverse effects. The panels met several times, beginning in June 1980.

The specific charge to the two panels was to determine:

- Whether the data available are sufficient to estimate the likelihood that the test chemicals have long-term health effects or delayed sequelae.

- Whether the involved chemicals, as tested, are likely to produce long-term adverse health effects or delayed sequelae in the test subjects.

ANTICHOLINESTERASE CHEMICALS

The panel concludes that although no evidence has been developed (to date) that any of the anticholinesterase test compounds surveyed carries long-range adverse human health effects in the doses used, the results of an ongoing NAS/NRC morbidity study may shed further light on this issue. The panel therefore is unable to rule out the possibility that some anti-ChE agents produced long-term adverse health effects in some individuals. Exposures to low doses of OP compounds have been reported (but not confirmed) to produce subtle changes in EEG, sleep state, and behavior that persist for at least a year. Whether the subjects at Edgewood incurred these changes and to what extent they might now show these effects are not known. If such changes occurred and persisted, they would be difficult to detect now. They could be determined scientifically only by a new study in which EEG, sleep state, and psychologic-test scores were compared with those from the NCT group. This might be considered, if reasonable suspicion develops, based on responses obtained in the ref- erenced morbidity study, that selected subjects experienced behavioral changes traceable in onset to experimental exposure to the anti-ChE agents.

ANTICHOLINERGIC CHEMICALS

No firm evidence has been seen that any of the anticholinergic test compounds surveyed produced long-range adverse human health effects in the doses used at Edgewood Arsenal. More intensive study is required to confirm this conclusion. The high frequency of uncontrolled variables makes evaluation of behavioral effects difficult.

On the basis of available data, in the judgment of the panel, it is unlikely that administration of these anticholinergic compounds will have long-term toxicity effects or delayed sequelae. An ongoing

morbidity study should provide more definitive information once it is completed.

MORTALITY

Standardized mortality ratios were derived from mortality data for the soldiers (all males) who participated in the Edgewood tests and from U.S. mortality rates. For each class of chemicals, the mortality rates among the soldiers were not significantly higher than the rates of the U.S. population, categorized by age and calendar year.

MORBIDITY

An ongoing morbidity study among the test subjects is expected to provide a more complete understanding of the long-term consequences of exposure to anticholinergic and anticholinesterase chemicals.

EXECUTIVE SUMMARY OF VOLUME 2

In 1980 the Board on Toxicology and Environmental Health Hazards of the National Research Council's Commission on Life Sciences began a program to evaluate the long-term health effects of chemical agents administered to military volunteers at the Army Chemical Center, Edgewood, Md., during the 1950s, 1960s, and 1970s. This work was conducted at the request of the Department of the Army. The tests were conducted to find out how various potential chemical warfare agents affect human performance. It was felt that animal tests were inadequate for this type of evaluation and that only humans could provide definitive information.

The first report (Volume 1) reviewed data on 15 anticholinesterase and 24 anticholinergic agents, to which almost half of some 6,700 subjects were exposed at Edgewood.

The current report, prepared by three panels of the Board's Committee on Toxicology, evaluates possible delayed health effects of three additional classes of compounds that were tested on most of the remaining volunteer subjects: cholinesterase reactivators, psychochemicals, and irritants and vesicants (blistering chemicals). The cholinesterase reactivators, of which there are four, are used as antidotes for anticholinesterase poisoning. The psychochemicals include phencyclidine, an anesthetic with substantial disorienting effects that is also available (with impurities) as the street drug PCP, and 10 related dibenzopyrans that are central nervous system depressants capable of producing orthostatic hypotension. The irritants include the well-known lacrimatory chemical CN, the riot-control agent CS, and other ocular and respiratory irritants. Mustard gas was the vesicant whose effects were studied.

The Committee established three panels to identify and assess evidence on the possible long-term health effects or delayed sequelae of the chemicals tested. As in the work that led to Volume 1, the chairman of each panel was selected from the Committee on Toxicology.

The specific charges to each panel were as follows:

- To determine whether there was sufficient evidence to assess the likelihood that the test chemicals had had long-term health effects or delayed sequelae.

- To determine on the basis of this evidence whether the chemicals, as administered, are likely to have produced such adverse effects in the test subjects.

The conclusions in this volume are based on available epidemiologic, toxicologic, and mortality data that were reported in Volume 1. They also rely on a review of test-subject exposure data obtained from Edgewood, all of which were available to panel members. Long-term clinical follow-up was not conducted. The subjects tested were healthier than the control subjects with whom they were compared, and both groups were healthier than the general population, reflecting the better health status of those in military service. The analyses presented here necessarily reflect the limitations of the available data. These conclusions might change in the light of information gained through a study of morbidity, which will be based on a questionnaire and an analysis of admissions to Army and Veterans' Administration hospitals (to be reported in Volume 3).

CHOLINESTERASE REACTIVATORS

On the basis of an examination of toxicologic literature, case reports from Edgewood volunteers, and a review of mortality data conducted by the National Research Council Medical Follow-up Agency, the Committee found no evidence of chronic disease in animals or humans associated with single or repeated doses of the cholinesterase reactivators (oximes). The lack of follow-up data on volunteers prevents certainty in predicting occurrence or absence of delayed effects. The compounds are eliminated very rapidly from the body, but they produce a variety of acute effects that are short-lived and reversible, such as gastrointestinal distress after oral administration, pain at an injection site, dizziness, headache, and ocular discomfort. The Committee found no conclusive studies of carcinogenicity, mutagenicity, teratogenicity, or reproductive anomalies associated with the four oximes and therefore did not reach a conclusion in this regard.

PSYCHOCHEMICALS

The Committee found the evidence on the long-term health effects of the tested psychochemicals to be sparse. The target organs that

may be involved in prolonged or delayed effects of phencyclidine are the brain and cardiovascular system. Target mental or cardiovascular effects did not take place within a week of exposure to the drug. No case reports have identified long-term effects or mental or cardiovascular effects soon after first exposure.

The margin of safety of a tested chemical is sometimes estimated by considering the ratio of the lethal dose to the pharmacologically effective dose (the dose at which some detectable biologic effect occurs). On the basis of animal data on the psychochemicals tested, the margin of safety for short-term effects is large for acute intravenous, intragastric, intraperitoneal, and subcutaneous administration and somewhat smaller for inhalation of the aerosolized form.

On the basis of the scientific literature alone, it is not possible to predict whether any long-term effects would be associated with the small exposures used. However, evaluation of this toxicity literature and the Edgewood studies led this Committee to conclude that, at the doses and frequencies of phencyclidine used at Edgewood in a small number of test subjects, it is unlikely that detectable long-term or delayed effects have occurred or will occur.

Acute administration of the dibenzopyrans (dimethylheptylpyran and congeners) produced various degrees of physical incapacitation in Edgewood subjects, mainly because of moderate to marked and prolonged orthostatic hypotension. The duration and intensity of effects varied among most doses and subjects. Despite the variations, there is a large pharmacologic margin of safety in the use of these compounds in animals. The dibenzopyrans produced more potent long-lasting orthostatic hypotension and weaker (but otherwise similar) psychologic effects than Δ-9-tetrahydrocannabinol during the Edgewood experiments. There is no information on chronic effects of dibenzopyrans.

IRRITANTS AND VESICANTS

The Committee analyzed published studies describing the in vivo and in vitro properties of the agents used and reviewed short-term data collected by the U.S. Army on volunteers. The ability to provide definitive answers to the questions raised by the charge to the Committee was limited by the absence of long-term follow-up studies of the soldiers and by the sparseness of chronic effects studies of these compounds in animals or in humans after industrial exposure.

In general, the Committee found insufficient evidence to evaluate these chemicals, except mustard gas. Mustard gas is an experimental mutagen and human carcinogen at high doses. Data on the irritants are insufficient to evaluate their mutagenicity, carcinogenicity, or other long-term effects. Tests of all these chemicals involved few exposures and low doses.

Mustard Gas (H)

Mustard gas is highly reactive and has vesicant and systemic toxic effects. It is an alkylating agent that is mutagenic in various laboratory test systems, including mammalian germ cells, but data are inadequate to predict the extent of its genetic risk in humans. Mustard gas is also carcinogenic in experimental animals and humans. Other possible long-term effects of mustard gas are related to its local toxicity; specifically, it can cause blindness, possible skin tumors from some cases of permanent scarring of the skin, and chronic bronchitis. Reported instances of long-term injury, such as carcinogenesis in workers in a Japanese mustard production plant, were associated with exposure at high, long-term dosages. Information is insufficient to project risks associated with smaller exposures to mustard gas; however, serious long-term adverse effects in the small number of soldiers who received one or a few low-dose exposures at Edgewood seem unlikely (except for possible skin tumors and some cases of permanent scarring). Some of those exposed at Edgewood suffered skin injuries that took several weeks to resolve. However, in view of the small number of persons tested (about 150 healthy men) and the very low dosages involved, it is unlikely that a statistically significant increase in the risk of cancer or other chronic disease can be detected in those exposed to mustard gas at Edgewood. When exposed, the Edgewood subjects were wearing gas masks and impregnated clothing--an ensemble being tested for efficacy against toxic contamination.

o-Chlorobenzylidene Malononitrile (CS)

Results of experimental studies in microorganisms and short-term experiments in laboratory animals suggest that long-term medical abnormalities in soldiers exposed to CS are unlikely. Acute tissue changes produced in animals and humans seem reversible and not likely to become chronic in the absence of recurrent exposures. Follow-up information on the long-term state of health of exposed soldiers is not available, but no reports indicate that Edgewood subjects have experienced any long-term sequelae.

Chloroacetophenone (CN)

CN, a moderately toxic irritant, has immediate effects on the eyes, skin, and respiratory tract. CN is a strong skin-sensitizing agent, but is rarely lethal. The Committee found no evidence of lasting ocular or respiratory effects in 99 volunteers exposed experimentally at Edgewood between 1958 and 1972 when subjects were evaluated 2 wk after cutaneous administration or inhalation of aerosol. Allergic contact dermatitis or hypersensitivity in these volunteers on re-exposure to CN is possible. There has been no systematic study of the possible mutagenic and neoplasm-promoting effects of CN with current scientific methods.

Dibenz[b,f][1,4]oxazepine (CR)

CR, a mild lacrimatory irritant, manifests less acute toxicity than CN and CS. At low doses, it causes transient effects. There are a few studies on long-term health effects, including potential mutagenicity and teratogenicity. The available data are insufficient to predict long-term health effects. The small number of exposures and the small number of subjects exposed to CR at low doses at Edgewood make the occurrence of demonstrable effects in these subjects unlikely.

Chloropicrin (PS)

PS is acutely toxic and has a variety of sensory effects in animals. It has not been evaluated thoroughly for mutagenicity or carcinogenicity. Like those exposed to mustard gas, the subjects exposed to PS were wearing gas masks, and small numbers of soldiers were exposed to small doses. PS is unlikely to have produced detectable long-term health effects in volunteers exposed at Edgewood.

Brombenzyl Cyanide (CA), Diphenylaminochlorarsine (DM), and 1-Methoxy-1,3,5-cycloheptatriene (CHT)

CA, DM, and CHT are unlikely to have produced measurable long-term health effects in volunteers exposed at Edgewood. But there are no specific toxicologic data on the mutagenicity and carcinogenicity of these compounds. CHT is less toxic than CN or DM when administered acutely.

Nonanoyl Morpholide

The Committee does not expect long-term health effects in volunteers tested with nonanoyl morpholide at the dosages used at Edgewood. As with CA, DM, and CHT, specific toxicologic data regarding its potential in this regard are not available.

123 Irritant Chemicals

A total of 123 irritant chemicals were tested on only two subjects each. There are no data on their mutagenicity, carcinogenicity, or other long-term health effects. However, because the exposures were small, detectable adverse effects seem unlikely.

OVERVIEW

The Army's studies on human subjects were designed entirely to evaluate short-term physiologic and pharmacologic effects. A review

of all available data reveals that these data are inadequate to provide definitive answers regarding the likelihood that the test chemicals produced or did not produce long-term health effects or delayed sequelae. Information on long-term health effects of the test chemicals on animals or humans is lacking, as is follow-up information on the current health status of the subjects. It therefore cannot be determined whether some subjects may have sustained long-term or delayed effects. Analysis of a questionnaire and of admissions to Army and Veterans' Administration hospitals (Volume 3) may provide further information on the current health status of these subjects.

APPENDIX B

UPDATED MORTALITY STUDY (SUMMARY)

by

Robert J. Keehn

The mortality analysis reported in Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents: Volume 1 was based on 12,195 chemical exposures reported by the Army, including 548 exposures to unclassifiable substances (chemicals of uncertain identity). Further searching by the Army has established the identity of most of the unclassifiable chemicals, reducing the number from 548 to 187. In its search, the Army found 1,454 tests that had not been included in the reported mortality analysis (see Table B-1). As a result, the total number of exposures has increased from the 20,851 of the reported mortality analysis to 22,305. Of the 1,454 additional exposures, 1,024 were to some chemical and 430 involved equipment testing without chemicals. Increases in numbers of exposures to the various types of chemicals range from zero (analgesics) to 379 (irritants and vesicants). Percentage increases in numbers of exposures were large in the cases of stimulants (356%), psychochemicals (185%), LSD derivatives (51%), and miscellaneous exposures (31%).

The number of volunteers who participated in the tests did not change. However, the reporting of 1,454 additional tests by the Army has changed the numbers of men in the various groups used in the mortality comparisons (Table B-2). The number of men who participated only in tests of equipment (no chemical exposure) decreased from 1,719 to 1,587. The number of men exposed to each class of chemicals, except the unclassifiable, increased; the numbers of participants exposed only to the cholinesterase reactivators, the irritants and vesicants, and the LSD derivatives increased; and numbers of participants exposed only to the anticholinesterases and the anticholinergics decreased.

The shifting of men and the corresponding deaths among the comparison groups necessitated that the experience be reanalyzed (Tables B-3 and B-4). The numbers of observed and expected deaths and the standard mortality ratios differ somewhat from those previously reported. But the conclusion in Volume 1 is unchanged: "It can be concluded that, over the time span examined here, there is no evidence that volunteer participation in the testing programs had any long-term adverse effect on mortality."

TABLE B-1

Numbers of Test Exposures Reported to the Army Initially and in Revision

Type of Exposure	No. Test Exposures Reported by Army: Initial Report	Revised Report	Change[a] No.	Change[a] %
Chemical	12,195	13,219	1,024	8.4
Anticholinesterase	1,697	1,820	123	7.2
Anticholinergic	2,656	2,739	83	3.1
Cholinesterase reactivator	1,004	1,072	68	6.8
Psychochemical (Sernyl)	40	114	74	185.0
Irritant or vesicant	2,482	2,861	379	15.3
Analgesic	47	47	0	0.0
Stimulant	18	82	64	355.6
Cannabinoid	259	260	1	0.4
Miscellaneous	118	155	37	31.4
LSD derivative	511	772	261	51.1
Innocuous chemical	502	562	60	12.0
Approved drug	1,636	1,786	150	9.2
Control substance	677	762	85	12.6
Unclassifiable	548	187	-361	-65.9
Equipment (no chemical)	8,656	9,086	430	5.0
Total	20,851	22,305	1,454	7.0

[a] From initially reported numbers; unclassifiable chemical exposures decreased, and all other categories except analgesics increased.

TABLE B-2

Numbers of Test Subjects Included in First and Second Mortality Analyses[a]

Type of Exposure	No. Subjects in First Analysis			No. Subjects in Second Analysis		
	Total	Only	Not Only	Total	Only	Not Only
Anticholinesterase	1,465	507	958	1,567	496	1,071
Anticholinergic	1,749	570	1,179	1,794	544	1,250
Cholinesterase reactivator	690	83	607	745	92	653
Psychochemical (Sernyl)	NI	NI	NI	NI	NI	NI
Irritant or vesicant	1,901	855	1,046	2,125	877	1,248
Analgesic	NI	NI	NI	NI	NI	NI
Stimulant	NI	NI	NI	NI	NI	NI
Cannabinoid	252	NI	NI	253	NI	NI
Miscellaneous	NI	NI	NI	NI	NI	NI
LSD derivative	NI	103	NI	NI	184	NI
Innocuous or control chemical	NI	106	NI	NI	101	NI
Approved drug	NI	159	NI	NI	160	NI
Unclassifiable	NI	NI	NI	NI	NI	NI
Equipment (no chemical)	NI	1,719	NI	NI	1,587	NI
Total	6,620	4,102	2,518	6,620	4,041	2,579

[a] NI = test group not included in mortality study.

TABLE B-3

Observed and Expected Deaths Among Test Subjects, by Chemical Group and Cause of Death

Underlying Cause of Death	Anticholinesterases[a]						Anticholinergics[a]						Cholinesterase Reactivators[a]					
	Only (N = 496)			Not Only (N = 1,071)			Only (N = 544)			Not Only (N = 1,250)			Only (N = 92)			Not Only (N = 653)		
	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E
All trauma[b]	7	11.5	0.61	17	22.3	0.76	13	9.5	1.37	11	22.0	0.50	3	1.7	1.76	11	12.0	0.92
Accidents	5	7.3	0.68	10	14.1	0.71	8	5.9	1.36	6	13.7	0.44	2	1.1	1.82	5	7.5	0.67
Homicide	1	1.8	0.56	4	3.5	1.14	4	1.5	2.67	2	3.5	0.57	1	0.3	3.33	4	1.9	2.11
Suicide	0	2.6	0.0	0	4.2	0.0	0	1.8	0.0	1	4.3	0.23	0	0.3	0.0	0	2.3	0.0
All diseases	12	17.4	0.69	12	25.5	0.47	5	7.5	0.67	7	16.5	0.42	2	1.7	1.18	6	11.2	0.54
Malignant neoplasms	6	3.9	1.54	5	5.7	0.88	1	1.7	0.59	3	3.6	0.83	0	0.4	0.0	3	2.5	1.20
Respiratory tract	2	1.1	1.82	2	1.4	1.43	0	0.3	0.0	2	0.7	2.86	0	0.1	0.0	1	0.6	1.67
Leukemia, aleukemia	0	0.3	0.0	2	0.5	4.00	0	0.2	0.0	0	0.4	0.0	0	0.0	[c]	2	0.2	10.00
Diseases, cardio-vascular system	5	7.4	0.68	5	9.9	0.51	4	2.6	1.54	1	5.5	0.18	0	0.6	0.0	1	4.1	0.24
Chronic nephritis, other renal	0	0.2	0.0	0	0.3	0.0	0	0.1	0.0	0	0.2	0.0	0	0.0	[c]	0	0.1	0.0
Total deaths, all causes[d]	20	28.9	0.69	35	47.8	0.73	21	17.0	1.24	22	38.5	0.57	5	3.4	1.47	19	23.2	0.82

TABLE B-3 (continued)

Underlying Cause of Death	Irritants and Vesicants[a]						Cannabinoids[a]			LSD Derivatives[a]					
	Only (N = 877)			Not Only (N = 1,248)			Total (N = 253)			Only (N = 184)			Not Only (N = 366)		
	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E
All trauma[b]	8	16.3	0.49	13	23.6	0.55	1	5.1	0.20	0	4.5	0.0	2	8.2	0.24
Accidents	5	10.1	0.50	9	14.8	0.61	1	3.2	0.31	0	2.9	0.0	1	5.2	0.19
Homicide	1	2.6	0.38	2	3.7	0.54	0	0.8	0.0	0	0.8	0.0	1	1.3	0.77
Suicide	1	3.1	0.32	2	4.5	0.44	0	1.0	0.0	0	0.8	0.0	0	1.5	0.0
All diseases	5	14.7	0.34	16	23.0	0.70	2	4.7	0.43	6	10.7	0.56	8	12.0	0.67
Malignant neoplasms	2	3.3	0.61	5	5.1	0.98	1	1.1	0.91	1	2.5	0.40	4	2.7	1.48
Respiratory tract	0	0.8	0.0	1	1.2	0.83	0	0.2	0.0	1	0.8	1.25	1	0.8	1.25
Leukemia, aleukemia	0	0.3	0.0	2	0.5	4.00	1	0.1	10.0	0	0.1	0.0	0	0.2	0.0
Diseases, cardio-vascular system	3	5.4	0.56	4	8.6	0.47	1	1.7	0.59	0	5.0	0.0	3	5.0	0.60
Chronic nephritis, other renal	0	0.2	0.0	0	0.3	0.0	0	0.1	0.0	0	0.1	0.0	0	0.1	0.0
Total deaths, all causes[d]	14	31.0	0.45	32	46.7	0.69	3	9.8	0.31	6	15.2	0.39	10	20.2	0.50

TABLE B-3 (continued)

Underlying Cause of Death	Drugs Only (N = 160)			Innocuous Chemicals and Controls Exclusively (N = 101)			No Test (N = 1,587)			Total Experience (N = 6,624)		
	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E	Obs.	Exp.	O/E
All trauma[b]	0	2.5	0.0	1	1.6	0.63	30	30.8	0.97	89	128.3	0.69
Accidents	0	1.6	0.0	1	1.0	1.00	20	19.4	1.03	57	80.6	0.71
Homicide	0	0.4	0.0	0	0.3	0.0	3	5.0	0.60	16	20.5	0.78
Suicide	0	0.5	0.0	0	0.3	0.0	2	5.8	0.34	5	24.1	0.21
All diseases	0	1.9	0.0	2	1.4	1.43	44	39.1	1.13	107	146.0	0.73
Malignant neoplasms	0	0.4	0.0	2	0.3	6.67	6	8.9	0.67	30	32.8	0.91
Respiratory tract	0	0.1	0.0	1	0.1	10.00	3	2.4	1.25	10	8.5	1.18
Leukemia, aleukemia	0	0.1	0.0	1	0.0	[c]	0	0.7	0.0	4	2.7	1.48
Diseases, cardiovascular system	0	0.7	0.0	0	0.5	0.0	21	16.0	1.31	42	57.7	0.73
Chronic nephritis, other renal	0	0.0	[c]	0	0.0	[c]	3	0.4	7.50	3	1.7	1.76
Total deaths, all causes[d]	2	4.5	0.44	4	3.1	1.29	84	70.0	1.20	222	274.3	0.81

[a] Only = subject received chemical of only this group, except for innocuous and control substances. Not Only = subject received chemical of this group and at least one other group of experimental chemicals.

[b] Includes undetermined injuries, whether accidental or purposely inflicted, and injuries resulting from operations of war.

[c] Indeterminate, because of zero denominator.

[d] Includes causes of death listed in this table, as yet undetermined causes, and all other causes.

TABLE B-4

Observed and Expected Deaths
Among Test Subjects, by Chemical

Chemical	No. Subjects	No. Deaths Observed	Expected	O/E
Anticholinesterase only	496	20	28.9	0.69
Sarin only	135	9	10.0	0.90
VX only	290	11	15.7	0.70
Remainder of group	71	0	3.2	0.0
Anticholinergic only	544	21	17.0	1.24
BZ only	102	5	5.4	0.93
EA 3443 only	27	1	1.1	0.91
EA 3580 only	38	0	1.1	0.0
Scopolamine only	58	4	1.4	2.86
Atropine only	40	3	1.3	2.31
EA 3834 only	56	1	1.1	0.91
Remainder of group	223	7	5.6	1.25
Irritant only	877	14	31.0	0.45
Mustard only	52	2	2.0	1.00
Remainder of group	825	12	29.0	0.41

APPENDIX C

INTERPRETABILITY OF FOLLOW-UP QUESTIONNAIRE DATA

The follow-up questionnaire was part of a concerted attempt to determine the nature, extent, and severity of protracted problems associated with exposure of volunteers to a variety of chemicals at the Edgewood test site. Considerable discussion and controversy attended the design and analysis problems. Of particular concern were the use of a specially constructed but untested questionnaire, the relatively small groups of men exposed to some chemicals, the sensitivity of the questionnaire for detecting the problems most probably associated with exposure, and the potential for causing extraordinary concern among the volunteer soldiers. Many specialists in questionnaire development were consulted regarding the types of information that might be elicited and the specific wording of questions. The resulting questionnaire was a compromise agreed on by the five panels and the National Research Council Committee on Use of Human Subjects. Several subjects of concern were not included in the final questionnaire, such as probes for specific symptoms, suicide attempts, diseases, treatments, behaviors, detailed history of later job-related exposure, accidents, and spontaneous abortions. An issue of great concern was the relatively small groups of men exposed to the psychochemicals and their effects on interpretability. Briefly stated, it was felt at the outset by the panel reviewing psychochemicals that data obtainable from a survey might add little to our understanding of the long-term health effects of chemicals tested.

POPULATION

The population to be followed was not contacted regularly after discharge from the Army and had not consented to or expected a follow-up attempt. It was therefore difficult to secure the cooperation and sample sizes desired to make the total response statistically useful. It is assumed that 6,395 of 6,720 soldiers were alive at the time of follow-up. Of those, 4,085 (64% of total or 82% of those located) responded to the questionnaire. Those who did not respond might not constitute a random sample of the entire population. It is possible that many of the nonrespondents failed to respond because they had nothing important to say. If that were true, it would strengthen our belief that long-lasting effects were generally not present. However, it is also possible that the nonrespondents had other reasons for failing to respond, such as

very low economic status, incarceration, and long-term hospitalization.

The importance of obtaining complete accounting of all those followed is shown by considering the numbers of subjects exposed to each drug. Large samples were exposed to the anticholinesterases, the anticholinergics, and the irritants and vesicants, but fewer than 100 were exposed to the psychochemical Sernyl. The loss of respondents in the smaller groups makes the conclusions for Sernyl more tentative, because of the statistical properties (i.e., power) of the comparison tests.

QUESTIONNAIRE DESIGN

Most of the problems associated with the questionnaire were due to a lack of explicit hypotheses as to potential long-term effects of the drugs studied. Questions of general interest were included, but specific hypotheses were not assessed with questions. Furthermore, the survey instrument was a questionnaire, not an interview. The questions therefore had to be simple, easily understood, and able to be answered quickly. Such constraints limit the specificity and detail of the information to be collected.

Even given those characteristics of the survey, some of the questions that were included could have been reworded or reconsidered. For example, the section on employment might have been longer and more complex than necessary; and the question as to children born to the subject could have indicated more clearly that unmarried subjects should report the numbers and sexes of their children.

OTHER CONSIDERATIONS

The climate in which the questionnaire was used might raise concern about interpretation of the results. For example, subjects who wished (for whatever reason) to misrepresent the nature and severity of their problems could distort the results (and hence their interpretation), especially if their chemical-test group was fairly small. In addition, as in any cohort study, there was no control of the subjects' environments after discharge from the service, so even legitimate complaints associated with exposure to toxic substances could have been due to occupational or accidental exposure to chemical agents, rather than to exposure at Edgewood.

SUMMARY

Some caution must be exercised in viewing the data obtained from the questionnaire. There were constraints on the information that

could have been gained on long-term effects of chemical exposure, even if follow-up had been conducted by personal interview with questions designed to test specific hypotheses. There were differences among the subjects exposed, including possible misrepresentation by subjects, variability in their lives after discharge, and an inherent difficulty of finding a representative follow-up sample after 10-30 years. Beyond these constraints, interpretation of the data that were collected entails additional problems. The data on general health, family, and work status are interpretable and appear to show good adjustment to civilian life by most of the men sampled. No major identifiable effects are observable in these data. However, the limited information available from the follow-up on these soldiers does not permit definitive conclusions regarding the nature and extent of possible long-term problems resulting from chemical exposure at Edgewood.

APPENDIX D

COHORT ADJUSTMENT OF FERTILITY FOR ANTICHOLINERGIC TEST GROUP, USING NO-CHEMICAL-TEST GROUP FOR COMPARISON

The following cohort evaluations of the anticholinergic test group were made with the "no chemical test" (NCT) group for comparison. (See Results section on family relationships for details of adjustments.) It should be cautioned that the NCT population is a peculiar comparison group for this purpose. The results, shown in Table D-1, are included for completeness.

Births to men tested with anticholinergics were fewer than would have been expected on the basis of the experience of the men in the NCT group. However, the deficit exists even for early births (before testing or not more than 1 year after test--births of children conceived before testing) and was even larger for such births than for later births. For the early period, the number of births (282) was only 73% of the number expected (384.3); the corresponding percentages for 2-4 years after testing, 5-7 years after testing, 8-10 years after testing, and more than 10 years after testing were 91%, 99%, 90%, and 109%. Therefore, the most likely explanation of the difference is that the selection process that assigned some volunteers to anticholinergic chemicals and others to no active chemicals (NCT), by whatever criteria were used, succeeded in distinguishing men who would have fewer children from those who would have more.

Not only was the number of births in the anticholinergic group low, but the male-to-female ratio among the children was low. It was also low among children conceived before testing. No satisfactory explanation is apparent, but the difference does not appear to be attributable to drug exposure.

TABLE D-1

Numbers and Sex of Offspring of Men Exposed
to Anticholinergics (Total),
by Year Since Testing and Expected Values,
Adjusted for Age and Year of Testing (NCT Group as Reference)

	No. Males		No. Females		Total[a]	
Time of Birth	Obs.	Exp.[b]	Obs.	Exp.[b]	Obs.	Exp.[b]
Before testing to 1 year after testing	138	209.0	140	167.0	282	384.3
2-4 years after testing	198	246.9	215	201.4	416	455.5
5-7 years after testing	223	284.2	276	222.2	509	514.6
8-10 years after testing	192	234.0	199	205.7	402	446.3
11+ years after testing	208	214.2	199	160.3	418	385.1
2 or more years after testing	821	979.3	889	789.6	1,745	1,801.5

[a] Total includes children of unknown sex.
[b] No-chemical-test (NCT) group used as standard for adjustment.

APPENDIX E

NATIONAL RESEARCH COUNCIL

COMMISSION ON LIFE SCIENCES

EXHIBIT A

2101 Constitution Avenue Washington, D.C 20418

MEDICAL FOLLOW-UP AGENCY

OFFICE LOCATION:
JOSEPH HENRY BUILDING
21ST STREET AND
PENNSYLVANIA AVENUE, N.W.
(202) 334-2825

Dear Sir:

The Medical Follow-up Agency of the National Academy of Sciences-National Research Council (a private, nongovernment research organization) is making a survey of the health status of men such as yourself who participated in studies conducted by the Army at the Aberdeen Proving Ground, Edgewood, Maryland, between 1955 and 1975.

To do the survey, we need accurate information that only you and the other participants can provide. Although you are under no formal obligation to answer our questions, we very much hope that you will complete and return the attached questionnaire.

You need not sign your questionnaire; the recorded study number will suffice to identify your reply. Although this study was initially suggested by the Congress, it is being sponsored by the Army in cooperation with the Veterans Administration. All personal information will be kept confidential. Your name and reply will not be made available to anyone outside of the Medical Follow-up Agency, and our report will deal with groups of men rather than with individuals.

If you wish to know the outcome of this study when it is completed, please check the appropriate box in the questionnaire.

When you have completed the accompanying questionnaire, please return it to me at the Medical Follow-up Agency. An addressed, postage-paid envelope is provided for your convenience.

Your cooperation is genuinely appreciated. Many thanks.

Sincerely,

Robert J. Keehn

Robert J. Keehn
Study Supervisor

RJK/mb
Enclosure

OMB No. 0702-0045
Expiration Date 12/31/84

HEALTH QUESTIONNAIRE

☐ **Check this box if you wish to be informed of the results of this study.**

1. What is your date of birth?

   (Month) _____ (Day) _____ (Year) _____

2. What was your Army service number (if you remember it)? _____

3. How much schooling have you completed? Check one answer.

   ☐ 1 Grade School (less than 6 years)
   ☐ 2 Grade School (6, 7, or 8 years)
   ☐ 3 High School, Incomplete (9, 10, or 11 years)
   ☐ 4 Completed High School (12 years)
   ☐ 5 College (13-16 years)
   ☐ 6 Graduate School (More than 16 years)

4. How would you rate your overall health? Check one answer.

   ☐ 1 Excellent ☐ 2 Good ☐ 3 Fair ☐ 4 Poor

5. a. What is your present marital status? (check one)

   ☐ 1 Married ☐ 2 Divorced ☐ 3 Separated ☐ 4 Widowed ☐ 5 Never married

   b. How many times have you been married? _____

   c. In what year were you married for the first time? _____ (year)

6. Please give the following information for each job you have had (including self-employment) since separation from active military service (record in order started):

   Date of separation ☐☐ (Month) ☐☐ (Year)

Order started	Full- or part-time job?	Date began job: Month	Date began job: Year	Date left job: Month	Date left job: Year	What did you do? (describe work)
1st	☐ 1 Full-time ☐ 2 Part-time	☐☐	☐☐	☐☐	☐☐	
2nd	☐ 1 Full-time ☐ 2 Part-time	☐☐	☐☐	☐☐	☐☐	
3rd	☐ 1 Full-time ☐ 2 Part-time	☐☐	☐☐	☐☐	☐☐	

Order started	Full- or part-time job?	Date began job: Month	Date began job: Year	Date left job: Month	Date left job: Year	What did you do? (describe work)
4th	☐ 1 Full-time ☐ 2 Part-time					
5th	☐ 1 Full-time ☐ 2 Part-time					
6th	☐ 1 Full-time ☐ 2 Part-time					

If you have more than six jobs to report, use space at end of questionnaire.

7. Which of the following statements *best* describes your present living arrangements? Check one statement.

☐ 1 Living with wife (room mate)
☐ 2 Living with parents (brother, sister)
☐ 3 Living with other adult(s)?
☐ 4 Living alone

8. Please give the following information for children you fathered who were alive at birth (answer starting with the first child born):

Order of	Sex	Date born, Mo. Yr.	Does this child have any physical or mental defects? (check, and if any, describe)	Is child now living?
1st (oldest)	☐ 1 Male ☐ 2 Female		☐ 1 No ☐ 2 Mental ☐ 3 Physical	☐ 1 Yes ☐ 2 No
2nd	☐ 1 Male ☐ 2 Female		☐ 1 No ☐ 2 Mental ☐ 3 Physical	☐ 1 Yes ☐ 2 No
3rd	☐ 1 Male ☐ 2 Female		☐ 1 No ☐ 2 Mental ☐ 3 Physical	☐ 1 Yes ☐ 2 No
4th	☐ 1 Male ☐ 2 Female		☐ 1 No ☐ 2 Mental ☐ 3 Physical	☐ 1 Yes ☐ 2 No

Order of	Sex	Date born, Mo. Yr.	Does this child have any physical or mental defects? (check, and if any, describe)	Is child now living?
5th	☐ 1 Male ☐ 2 Female	☐☐ ☐☐	☐ 1 No ☐ 2 Mental ☐ 3 Physical	☐ 1 Yes ☐ 2 No
6th	☐ 1 Male ☐ 2 Female	☐☐ ☐☐	☐ 1 No ☐ 2 Mental ☐ 3 Physical	☐ 1 Yes ☐ 2 No

If you have more than six children to report, use space at the end of questionnaire.

9. Have you ever had a health problem a health professional (doctor, nurse, etc.) said was caused by exposure to toxic or poisonous substances?

☐ 1 No ☐ 2 Yes (If Yes, name substance(s), describe the problem, tell when and how it was treated, and the result) _____

_____

_____

10. a. Have you smoked a total of 100 or more cigarettes (5 packs) in your entire life?

☐ 1 No (go to question 11) ☐ 2 Yes

b. Have you ever smoked tobacco in any form regularly (daily, more than occasional smoking)?

☐ 1 No (go to question 11) ☐ 2 Yes

c. At what age did you start regular smoking? _____

d. During the past month, how much did you smoke on a typical day? (please record your daily consumption for *each* form of tobacco):

Cigarettes, number of *packs* daily _____ Pipes, number of pipefuls daily _____

Cigars, number daily _____ ☐ 000 I no longer smoke.

e. Did you ever stop smoking for more than one year? ☐ 1 No ☐ 2 Yes

If yes, for how many years, total? _____

11. a. During the past year what was your daily consumption of alcohol?

☐ 0 None ☐ 1 Some (for *each* beverage listed below, circle your usual number of drinks per day)

Beer	less than 1	1-2	3-4	5 or more	drinks per day
Wine	less than 1	1-2	3-4	5 or more	drinks per day
Whiskey or other hard liquor	less than 1	1-2	3-4	5 or more	drinks per day

11. b. Have you ever been treated for alcoholism or for any health problem due to drinking?

☐ No (1) ☐ Yes (If Yes, explain) (2) _____

_____

_____

12. How many times EVER have you used or been given *each* of the following substances? Circle one answer, A, B, C, D, or E, for each substance.

Substance	Never	1-9 times	10-99 times	100-999 times	1000 or more times
Amphetamines or other stimulants (speed, STP, uppers, etc.)	A	B	C	D	E
Barbiturates or other depressants (barbs, downers, Quaalude, ludes, sopor, etc.)	A	B	C	D	E
Cocaine (coke)	A	B	C	D	E
Heroin (H, horse, smack)	A	B	C	D	E
LSD (acid)	A	B	C	D	E
Marijuana (grass, hashish, hemp, pot)	A	B	C	D	E
Phencyclidine (PCP, angel dust)	A	B	C	D	E
Other narcotics, opiates (opium, morphine, codeine, methadone, Demerol, Darvon, etc.)	A	B	C	D	E
Tranquilizers (Miltown, Librium, Valium, Thorazine, etc.)	A	B	C	D	E

13. a. During the past five years have you had medical care for any disease or illness?

☐ No (1) ☐ Yes (2) (If Yes, state nature of illness)_____

_____

b. During the past five years have you been admitted to a hospital for more than an overnight stay?

☐ No (1) ☐ Yes (2) (If Yes, state nature of illness) _____

_____

14. During the past *month*, did an illness or injury keep you in bed for all or most of a day?

☐ No (1) ☐ Yes (2) If Yes, how many days were you kept in bed? _____

What was the matter? _____

15. a. Answer *each* of the six endings to this question. Does any impairment or health problem–

1) keep you from working at a job or business?	☐ No 1	☐ Yes 2
2) limit the kind or amount of work you can do?	☐ No 1	☐ Yes 2
3) keep you from doing any household chores at all?	☐ No 1	☐ Yes 2
4) limit the kind or amount of household chores you can do?	☐ No 1	☐ Yes 2
5) cause you to need the help of other persons with your personal care needs, such as eating, bathing, dressing, getting around the home?	☐ No 1	☐ Yes 2
6) cause you to need the help of other persons in handling your routine needs, such as everyday household chores, doing necessary business, shopping, getting around for other purposes?	☐ No 1	☐ Yes 2

If you answered "Yes" to ANY of the six questions in Part a above, continue by answering Parts b and c, below. If all six answers are "No", skip Parts b and c.

b. In what ways are your activities limited? Describe _____

_____

c. What condition would you say is the MAIN cause of this limitation? Specify _____

_____

May we phone you for further details?

(___)_____ Phone number (include area code)

If you need additional space to complete your reply to any question, or wish to make any additional comments, please attach extra pages as needed. (Please indicate question number of responses being continued)

APPENDIX E

EXHIBIT B

NATIONAL RESEARCH COUNCIL
COMMISSION ON LIFE SCIENCES
2101 Constitution Avenue Washington, D.C. 20418

MEDICAL FOLLOW-UP AGENCY

OFFICE LOCATION:
JOSEPH HENRY BUILDING
21ST STREET AND
PENNSYLVANIA AVENUE, N. W.
(202) 334-2825

Several weeks ago we wrote to you, copy enclosed, requesting information concerning your health. We hope that your failure to reply was not an oversight and that we shall hear from you soon.

It is of great importance that we receive your reply. We hope that you have no past or present health problems to report, but we cannot know that this is true unless you tell us so. Your contribution to the success of this survey will more than justify the few minutes of your time required to answer our questions. You have our assurance that all information you give us will be kept confidential.

Please complete the accompanying questionnaire and return it to me, using the addressed envelope provided for your convenience. No postage is needed. Your cooperation is much appreciated.

Sincerely,

Robert J. Keehn
Study Supervisor

RJK/mb
Enclosures

APPENDIX E

NATIONAL RESEARCH COUNCIL
COMMISSION ON LIFE SCIENCES
2101 Constitution Avenue Washington, D.C. 20418

MEDICAL FOLLOW-UP AGENCY

OFFICE LOCATION:
JOSEPH HENRY BUILDING
21ST STREET AND
PENNSYLVANIA AVENUE, N.W.
(202) 334-2825

EXHIBIT C

This third request for information concerning your health has been sent by certified mail so that we will know that it has been delivered to you and that our lack of a reply to the earlier requests was not due to a wrong address.

You are one of a small group of men whose health is being studied. You are special in that you alone can provide the information we need. Please take a few minutes of your time to send your answers to our questions. An addressed, no-postage-required envelope is enclosed for your convenience.

Should you have any questions, please call me collect, person-to-person, Monday through Friday, between 8:30 a.m. and 4:00 p.m., Eastern Time. The number is (202) 334-2825. If you still decide not to answer our questions, please return the blank questionnaire. We hope that you will tell us why you are returning the questionnaire unanswered.

Sincerely,

Robert J. Keenn

Robert J. Keenn
Study Supervisor

RJK/mb
Enclosure

EXHIBIT D

MA 24 WASH DC 8/3/84
ZIP

OHATCHEE AL 3627]

YOU WILL SOON RECEIVE A THIRD REQUEST FROM THE NATIONAL RESEARCH COUNCIL FOR THE ANSWERS TO A FEW QUESTIONS MAILED TO MEN WHO PARTICIPATED IN THE SERIES OF TESTS CONDUCTED BY THE ARMY AT EDGEWOOD, MARYLAND. MOST HAVE REPLIED AND HAVE REQUESTED A SUMMARY OF FINDINGS WHEN THE SURVEY IS COMPLETED. WE ARE ANXIOUS TO HAVE YOUR PROMPT REPLY.

WHILE MOST HAVE ALREADY RESPONDED, THE SURVEY WILL BE INCOMPLETE WITHOUT YOUR REPLY. IT IS IMPORTANT THAT EVERY MAN TAKE PART.

SINCERELY,

ROBERT J. KEEHN
STUDY SUPERVISOR

APPENDIX E

Figure II-4

NATIONAL RESEARCH COUNCIL NONRESPONSE SURVEY RTI PROJECT NO. 3166

EXHIBIT E

A. IDENTIFYING INFORMATION

09999

Doe, John
Box 123
Hoboken, NJ 41224
511766272
511210

Telephone Interviewer Number

1 _____
2 _____
3 _____
4 _____

B. SCREENING QUESTIONS

"Hello, may I speak with "_____name on label_____?" (If respondent is reached, proceed to introduction and questionnaire on the back.) If respondent is not reached, verify the number you dialed. If the number is correct, ask the person you are talking with, "Do you know _____name on label_____, or how I can get in touch with him/her?" Record any information they volunteer and thank them for their time. If the person does not know respondent, thank them for their time and record the appropriate code.

C. RECORD OF CALLS AND COMMENTS

Call No.	Date	Time	Person Contacted	Result Code	Notes
1					
2					
3					
4					
5					
6					

D. RESULT CODES

Temporary Codes

1 = Ring, No Answer
2 = Busy Signal
3 = Unable to Locate/Contact Respondent
4 = Respondent Not Available
5 = Appointment Made
6 = Breakoff/Partial Data
7 = Language Barrier
8 = Other (explain in notes)

Final Codes

11 = Interview Complete
12 = Breakoff/Partial Data
13 = Refusal
14 = Language Barrier
15 = Physically/Mentally Incompetent
16 = Unable to Locate/Contact Respondent
17 = Other (explain in notes)

E. INTRODUCTION -- Read only when named respondent is on the line.

Hello, my name is _____ and I'm calling from the Research Triangle Institute in N.C. We have been asked by the National Research Council located in Washington, D.C. to contact veterans who, from their records, were on special assignment at the Aberdeen Proving Ground located in Edgewood, Maryland during their military term. I have a few questions that I would like to ask you that will only take a few minutes of your time. However, before I begin, I want to tell you that:

- you don't have to answer any questions you don't want to,
- you can stop me at any time,
- there will be no harm or benefit to you from answering these questions, and
- your name and answers will not be revealed to anyone other than authorized project staff.

So I would like to begin with the first question.

F. QUESTIONNAIRE

1. While in the military service, do you recall being sent to the Aberdeen Proving Ground in Edgewood, Maryland for special duty between 1955 and 1975?

☐ Yes ☐ No [STOP] ☐ Never in service [STOP]

2. Do you remember receiving a health survey questionnaire in the mail recently from the National Research Council?

☐ Yes ☐ No [STOP]

3. Did you reply as requested?

☐ Yes [STOP] ☐ No

4. I want to read a few reasons that might explain why you didn't reply to the questionnaire. Please tell me all that apply for you. (CIRCLE ALL THAT APPLY)

a. You didn't have any health problems to report.
b. You felt the questions were too personal.
c. You were concerned about confidentiality.
d. You felt the questionnaire was too long.
e. You felt the questionnaire was too difficult.
f. You didn't participate in the test program due to your change of mind or rejection on the part of the military.
g. Are there any other reasons? (SPECIFY) _____

_____

_____

I want to thank you for your time and cooperation. Goodbye.